

FDA Briefing Document

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

November 24-25, 2014

Epidural Steroid Injections (ESI) and the Risk of Serious Neurologic Adverse Reactions

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the administration of epidural steroid injections (ESI) and the risk of serious neurologic adverse reactions to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Anesthetic and Analgesic Drug Products Advisory
Committee Meeting**

Epidural Steroid Injections (ESI) and the Risk of Serious Neurologic Adverse Reactions
November 24-25, 2014

**Briefing Materials
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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products

MEMORANDUM

Date: October 29, 2014

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To: Chair, Members, and Invited Guests

Re: Overview of the November 24-25, 2014 Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee to Discuss the risk of serious neurologic adverse reactions associated with epidural steroid injections.

Epidural injection of corticosteroids is a common procedure performed in the United States for the management of radicular pain associated with pain related to the spine. However, CDER has never approved an injectable corticosteroid product for administration via epidural injection.

Because injectable corticosteroids are not FDA-approved for this route of administration, the epidural injection of corticosteroids is considered an “off-label” use. Off-label use of medication is common and part of the practice of medicine; however, off-label use introduces challenges in determining the risk-benefit balance of a medication. In addition, the procedural aspects of epidural injections may have implications on the risk of serious neurologic events and can complicate assessing the role of the corticosteroid in the adverse event.

The document that follows will provide the background and regulatory history for this safety issue, summarize findings from the Agency’s reviews, and the topics for discussion for the upcoming meeting. Specifically, detailed information about the following aspects of this issue will be provided:

1. Background and Regulatory History
2. The use of epidural steroid injections (ESI) in the management of spinal pain syndromes
3. An overview of the efficacy data reported in the literature and limitations of the studies conducted to collect those data
4. Summaries of the safety data in animals and humans for this use of corticosteroids, based on FDA’s review of the literature and the FDA Adverse Event Reporting System
5. Estimates of the frequency of ESI
6. Background on FDA’s Safe Use Initiative and information about the expert panel convened to make recommendations for safe use of ESI
7. Regulatory Requirements and Guidance Recommendations for the Relevant Sections of the Product Labeling

At the meeting, you will be asked to discuss the risk of serious neurologic adverse reactions associated with ESI administered to reduce inflammation for pain management. The committee will also be asked to consider the efficacy of ESI and the overall risk-benefit balance of injecting steroids in the epidural space to treat pain.

Again, we are grateful for your participation in this meeting and thank you for providing your expertise and insight. We are hopeful that your discussions and deliberations at this meeting will assist us in determining possible regulatory options, including, but not limited to, changes to the product labeling.

Draft Points to Consider

1. Discuss your understanding of the benefits of epidural corticosteroid injection for the treatment of spinal pain. Considerations in the discussion may include the following:
 - a. Medical condition being treated
 - b. Location of the injection
 - c. Injection approach
 - d. Corticosteroid formulation
2. Discuss your understanding of the risks of epidural corticosteroid injection for the treatment of spinal pain, particularly the potential neurological sequelae. Considerations in the discussion may include the four factors listed in question 1 above.
3. Based on your discussions of the benefits and risks of epidural corticosteroid injection for the treatment of spinal pain, do you recommend any modifications to class labeling (e.g., Boxed Warning, Contraindication, modifications to the Warning statement)?

Discuss the rationale for your response and any important details to include in the labeling.
4. Discuss any additional recommendations you have on this topic.

Epidural Steroid Injections (ESI) and the Risk of Serious Neurologic Adverse Reactions

Integrated Summary Memorandum

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1 Introduction

Thank you for your participation in the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting to be held on November 24-25, 2014. As participants in the AADPAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the FDA) on various regulatory decisions. The upcoming meeting is being held to discuss the risk of serious neurologic adverse reactions associated with epidural steroid injections (ESI) administered to reduce inflammation for pain management. The committee will also consider the efficacy of ESI and the overall risk-benefit balance of injecting steroids in the epidural space to treat pain. These considerations will assist the FDA in our discussions of possible regulatory options, including but not limited to changes to the product labeling.

Epidural injection of corticosteroids is a common procedure performed in the United States for management of spinal pain. However, CDER has never approved an injectable corticosteroid product for administration via epidural injection. Because injectable corticosteroids are not FDA-approved for this route of administration, the epidural injection of corticosteroids is considered an “off-label” use. Off-label use of medication is common and part of the practice of medicine; however, off-label use introduces challenges in determining the risk-benefit balance of a medication. In addition, the procedural aspects of epidural injections may have implications on the risk of serious neurologic events and can complicate assessing the role of the corticosteroid in the adverse event.

As described in the Regulatory History below, the FDA has been evaluating the issue of serious neurologic events with ESI since 2009 and the FDA’s Safe Use Initiative (SUI)^[A] convened an external expert panel in 2011 to work on this issue (See Section 8 below). Although FDA does not regulate epidural injections, FDA does regulate medications that are injected during this procedure. FDA can require manufacturers of corticosteroids to add safety information to product labels, even if the safety information is related to off-label use. Recently the FDA required a class Warning on injectable corticosteroids to include information about the risk of serious neurologic events with ESI^[B] (See Attachment 1). The purpose of this Advisory Committee meeting is to discuss this safety issue and seek further recommendations for the FDA from the Advisory Committee panel.

In this summary memorandum, information about the following aspects of this issue will be provided to serve as starting points for the discussions that will take place during this Advisory Committee meeting and the formulation of your answers to the questions posed by the FDA:

1. Background and Regulatory History

2. The use of epidural steroid injections (ESI) in the management of spinal pain syndromes
3. An overview of the efficacy data reported in the literature and limitations of the studies conducted to collect those data
4. Summaries of the safety data in animals and humans for this use of corticosteroids, based on FDA's review of the literature and the FDA Adverse Event Reporting System (FAERS)
5. Estimates of the frequency of ESI
6. Background on FDA's Safe Use Initiative and information about the expert panel convened to make recommendations for safe use of ESI
7. Regulatory Requirements and Guidance Recommendations for the Relevant Sections of the Product Labeling

2 Regulatory History

In November 2009, Dr. James Rathmell, an anesthesiologist at Massachusetts General Hospital, contacted the FDA regarding the use of depot formulations of steroids for transforaminal epidural injections and the risk of catastrophic neurologic injuries. Based upon this inquiry, the FDA initiated a safety review of serious neurologic events with ESI.^[C] The safety review included a review of the FDA Adverse Event Reporting System (FAERS) and reports in the published literature associated with the five corticosteroid products marketed for injection: betamethasone, dexamethasone, hydrocortisone, methylprednisolone, and triamcinolone. The review team noted the serious nature of some of the post-marketing reports, including stroke, paraplegia, quadriplegia, and spinal cord infarction, and also recognized that epidural injection was an off-label use of corticosteroids. A summary of the FAERS data will be described elsewhere in this document (see Section 5 and Attachments 2, 3, 4, and 5).

The findings of this review led the FDA to determine how best to address this safety issue while taking into account that ESI are widely utilized in the practice of medicine to treat painful conditions, which are common in the population, greatly affect the quality of life for the patients, and have a considerable impact on society as well. The safety review team initially recommended that a class Warning be added to the injectable corticosteroid product labels. This proposal was presented to FDA's Drug Safety Oversight Board (DSB) in September 2010. The DSB is a panel of federal partners (AHRQ, CDC, CMS, DOD, HRSA, IHS, NIH, and VA) that advises the FDA's Center for Drug Evaluation and Research (CDER) on how to address important drug safety issues.^[D] The DSB raised concerns about the potential for unintended consequences of the proposed class Warning for the injectable corticosteroids given that patients may be considering alternatives for pain management such as opioid therapy or surgery that carry their own inherent risks. The DSB also noted factors that add to the complexity of understanding the cause of the safety issue, e.g., the injection technique and location of the injection.

Because of the feedback from the DSB and based on additional internal discussion in CDER, the FDA decided that the FDA's Safe Use Initiative (SUI)^[A] would be appropriate to address this safety issue. The FDA's Safe Use Initiative was created to facilitate public and private collaborations within the healthcare community. The goal of the Safe Use Initiative is to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing, and evaluating cross-sector interventions with partners who are committed to safe medication use. The SUI convened a panel of experts on the topic and has been working on the issue with them since 2011. Additional details of the SUI process will be discussed in more detail in Section 8 of this document.

In the interim, in October 2010, Bristol-Myers Squibb submitted labeling supplements for Kenalog-10 and Kenalog-40 Injection (triamcinolone acetonide injectable suspension) for the

following: 1) to add 'Not for Epidural or Intrathecal Use' to the beginning of the product labeling and 2) to modify an existing Warning statement about intrathecal use to incorporate information about epidural use.^[E] These labeling supplements were approved in June 2011. Given the ongoing work by SUI, this labeling was not requested or required for other injectable corticosteroids.

During 2012 and 2013, members of an organization called "Arachnoiditis Society for Awareness and Prevention" contacted the FDA regarding the safety of ESI. This group has an interest in the FDA's ongoing review of the safety of ESI.

In 2014, because of additional concern about the neurological risks of ESI, the FDA required a class Warning to be added to the product labels for injectable corticosteroid products to ensure that healthcare providers are aware of the potential risk of serious neurologic events with ESI and to remind healthcare providers that the FDA has not approved corticosteroids for epidural injection. At the time the class Warning statement was announced in an FDA Drug Safety Communication (April 2014), FDA also committed to holding an Advisory Committee meeting to determine whether additional regulatory action is needed on this issue.^[B] The class Warning language is shown below:

WARNING

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids (see **WARNINGS: Neurologic**). Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

A number of injectable corticosteroids are approved either as branded New Drug Application (NDA) products or generic Abbreviated New Drug Application (ANDA) products. The following list shows the approved NDAs for injectable corticosteroids, but note that not all of these products may be commercially available.^[F] These products were required to update their product labeling to incorporate the new Warning.

- betamethasone acetate; betamethasone sodium phosphate
 - NDA 14602 (Celestone Soluspan by Merck Sharp Dohme)
- dexamethasone sodium phosphate
 - ANDAs only
- hydrocortisone sodium succinate
 - NDA 9866 (Solu-Cortef by Pharmacia and Upjohn [Pfizer])
- methylprednisolone acetate

- NDA 11757 (Depo-Medrol by Pharmacia and Upjohn [Pfizer])
- methylprednisolone sodium succinate
 - NDA 11856 (Solu-Medrol by Pharmacia and Upjohn [Pfizer])
- triamcinolone acetonide
 - NDA 12041 and 14901 (Kenalog-10 and Kenalog-40 by ApotHEcon [Bristol Myers Squibb])
- triamcinolone hexacetonide
 - NDA 16466 (Aristospan by Sandoz)

Throughout the remainder of this document, the safety issue is described in more detail. Although the FDA has updated the corticosteroid product labeling to include safety information on ESI, the Advisory Committee panel will discuss whether further regulatory activities are recommended.

3 Overview of Epidural Steroid Injections (ESI) for the Management of Pain Syndromes

Back pain is the most common of all chronic pain disorders with lifetime prevalence reported to be 54-80%. It is not uncommon for radicular pain to occur in conjunction with back pain, e.g., cervical radiculopathy with neck pain and sciatica with lower back pain. ESI for managing these types of chronic pain are one of the most commonly performed interventions in the United States. See Section 7 of this document for estimates of the frequency of ESI.

Epidural steroid injections are performed in the office setting, hospitals, and surgery centers by a variety of healthcare providers, including anesthesiologists, nurse anesthetists, radiologists, neurologists, physiatrists, and surgeons. Fluoroscopy is frequently used for guidance during needle insertion and, along with the injection of contrast media, to confirm needle location prior to injection of the corticosteroid, which is often mixed with a local anesthetic that is used to confirm deposition of the corticosteroid near the affected nerves.

3.1 Features of injectable corticosteroids

In the published literature about ESI, the different corticosteroids are often classified as ‘particulate’ or ‘non-particulate’. This classification is noteworthy, because throughout the published literature there are assertions that different types of corticosteroids (particulate vs. non-particulate) have an impact on the efficacy and safety of ESI. The specific definition for ‘particulate’ and ‘non-particulate’ is not clear, but appears to be based upon particle size. The FDA does not have definitions for ‘particulate’ and ‘non-particulate’ and does not use these categories to classify injectable corticosteroids. Instead, the FDA describes injectable corticosteroids as solutions or suspensions, but these categories may not necessarily correspond to the literature categories of non-particulate vs. particulate. The different injectable corticosteroids are shown in Table 1 below with information from FDA-approved product labeling regarding solubility, excipients, and suspension vs. solution. Some excipients were noted because of the potential impact on safety, e.g. potential neurotoxicity of benzyl alcohol.

Table 1. Information about FDA-approved injectable corticosteroids

Corticosteroid	Tradename	Sponsor	Suspension or Solution	Solubility in in H ₂ O	Notable Excipients
Betamethasone acetate, betamethasone sodium phosphate	Celestone Soluspan	Merck Sharpe Dohme	Suspension	acetate form insoluble; sodium phosphate form soluble	Benkalkonium Chloride
Dexamethasone sodium phosphate	Generic only	Multiple	Solution	freely soluble	Benzyl Alcohol

Hydrocortisone sodium succinate	Solu-Cortef	Pharmacia and Upjohn (Pfizer)	Powder for solution	very soluble	
Methylprednisolone acetate	Depo-Medrol	Pharmacia and Upjohn (Pfizer)	Suspension		Benzyl Alcohol Polyethylene Glycol
Methylprednisolone sodium succinate	Solu-Medrol	Pharmacia and Upjohn (Pfizer)	Powder for solution	soluble	+/- Benzyl Alcohol
Triamcinolone acetonide	Kenalog-10 Kenalog-40	Bristol Myers Squibb	Suspension		Benzyl Alcohol
Triamcinolone Hexacetonide	Aristospan	Sandoz	Suspension		Benzyl Alcohol

These steroids are synthetic derivatives of the endogenous hormones of the adrenal cortex (e.g., cortisol, or hydrocortisone when formulated as a drug) and have varying degrees of aqueous solubility. Generally, synthetic corticosteroids are lipophilic and would generally be formulated as suspensions (e.g., triamcinolone acetonide, triamcinolone hexacetonide, methylprednisolone acetate, betamethasone acetate). But if the corticosteroids are derivatized to include a salt moiety in their structure (betamethasone sodium phosphate, dexamethasone sodium phosphate, methylprednisolone sodium succinate), they become water soluble and formulations are generally solutions.

Researchers have performed microscopic analysis of several corticosteroid formulations to evaluate particulate shape, size, and aggregation.[1;2] The authors noted that triamcinolone acetate and methylprednisolone acetate tended to coalesce into large aggregates, but dexamethasone generally did not have particles. Betamethasone is more complicated because the FDA-approved formulation has both a soluble (salt) and insoluble (ester) component and depending on the formulation of betamethasone analyzed, the microscopic analysis and particle size could be different.

It is conceivable that the corticosteroid formulation could impact efficacy. For example, an ester formulation that requires hydrolysis to release the active moiety may have longer time to onset of action, but longer duration of effect.[3] In addition to efficacy considerations, with suspension formulated steroids for injection, particle size/aggregation are likely important parameters to consider due to the potential for embolism and infarction.[3-6]

It should also be noted that in addition to the FDA approved injectable corticosteroids, FDA acknowledges the availability of compounded corticosteroids for injection that are being used for ESI. The preparation of these products may impact the safety of ESI.^[G] Compounding is not a topic for discussion at this meeting.

One of the issues that may be raised at the AC meeting is whether the risk of serious neurologic events differs with different corticosteroids. There are reports in the literature that there is an increased risk of serious neurologic events with particulate corticosteroids compared to non-particulate corticosteroids, and there have been criticisms of the FDA for requiring a Warning on all the corticosteroids.^[H][7] These assertions are challenging for the FDA for several reasons. As noted above, FDA does not categorize corticosteroids as ‘particulate’ or ‘non-particulate’. In addition, it is difficult to compare event rates based upon spontaneous post-marketing reports, and the use patterns of ‘particulate’ or ‘non-particulate’ corticosteroids may vary. Finally, the level of evidence needed to support labeling one or more corticosteroids as safer than another would be quite high.

3.2 Approaches for ESIs

In addition to the variety of corticosteroid products available, there are several approaches utilized for epidural injections including: interlaminar, transforaminal, and caudal. The approach used is determined by the type of pain being treated, the anatomic area where the steroid deposition is to occur, and the level of comfort the treating clinician has with each of the injection approaches. The approach used may impact the risks for intravascular or intrathecal injection.

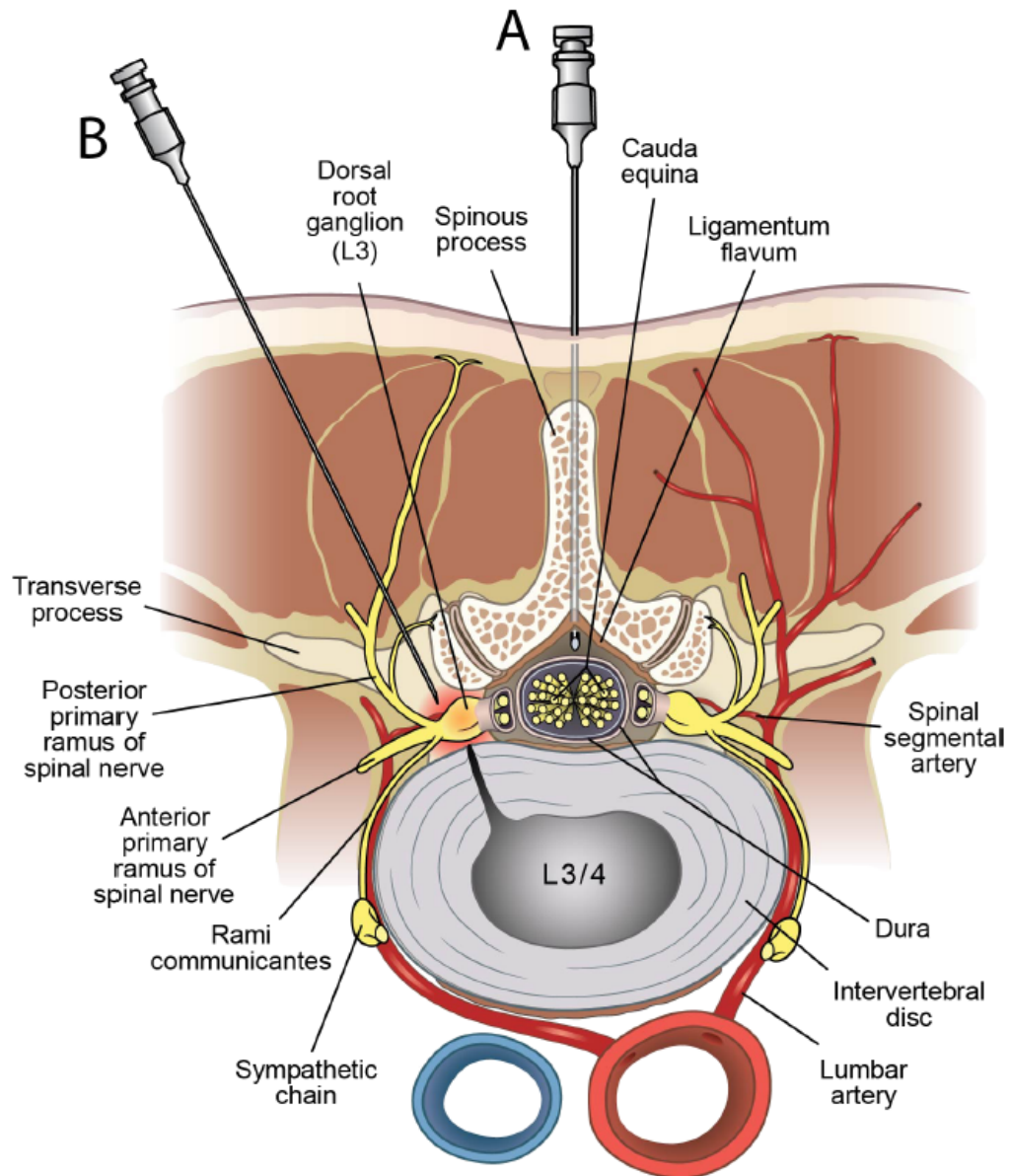
The interlaminar injections are performed by inserting the needle between (midline), or adjacent and parallel to (paramedian), the spinous processes of two vertebrae and traversing the ligamentum flavum to the epidural space. (See Figure 1, position A)

The transforaminal approach to the epidural space is generally done using fluoroscopy to identify the bony landmarks and confirm the injectate reaches the epidural space. The needle is inserted into the skin over the lateral border of and approximately halfway between two adjacent transverse processes at the interspace where the injectate is to be administered. The needle is advanced toward the lower edge of the transverse process, near its junction with the superior articular process. The needle is then directed towards the superior, lateral, anterior aspect of the neural foramen. The goal is to position the needle in the triangle composed of the pedicle, the nerve root, and the vertebral body. (See Figure1, position B)

A caudal injection is placed through the sacral hiatus. The needle is advanced into the caudal canal to a point 1-2 cm beyond and posterior to the ventral plate of the sacrum. A catheter

may be passed through the needle at this juncture to permit more cephalad injection of the medications.

Figure 1. Approaches for epidural injections: “A” demonstrates the interlaminar route of administration; “B” represents the transforaminal route. [Figure 1, p. 177, from Cohen et al.[8]]



4 Overview of Evidence Relating to the Efficacy of Epidural Steroid Injections

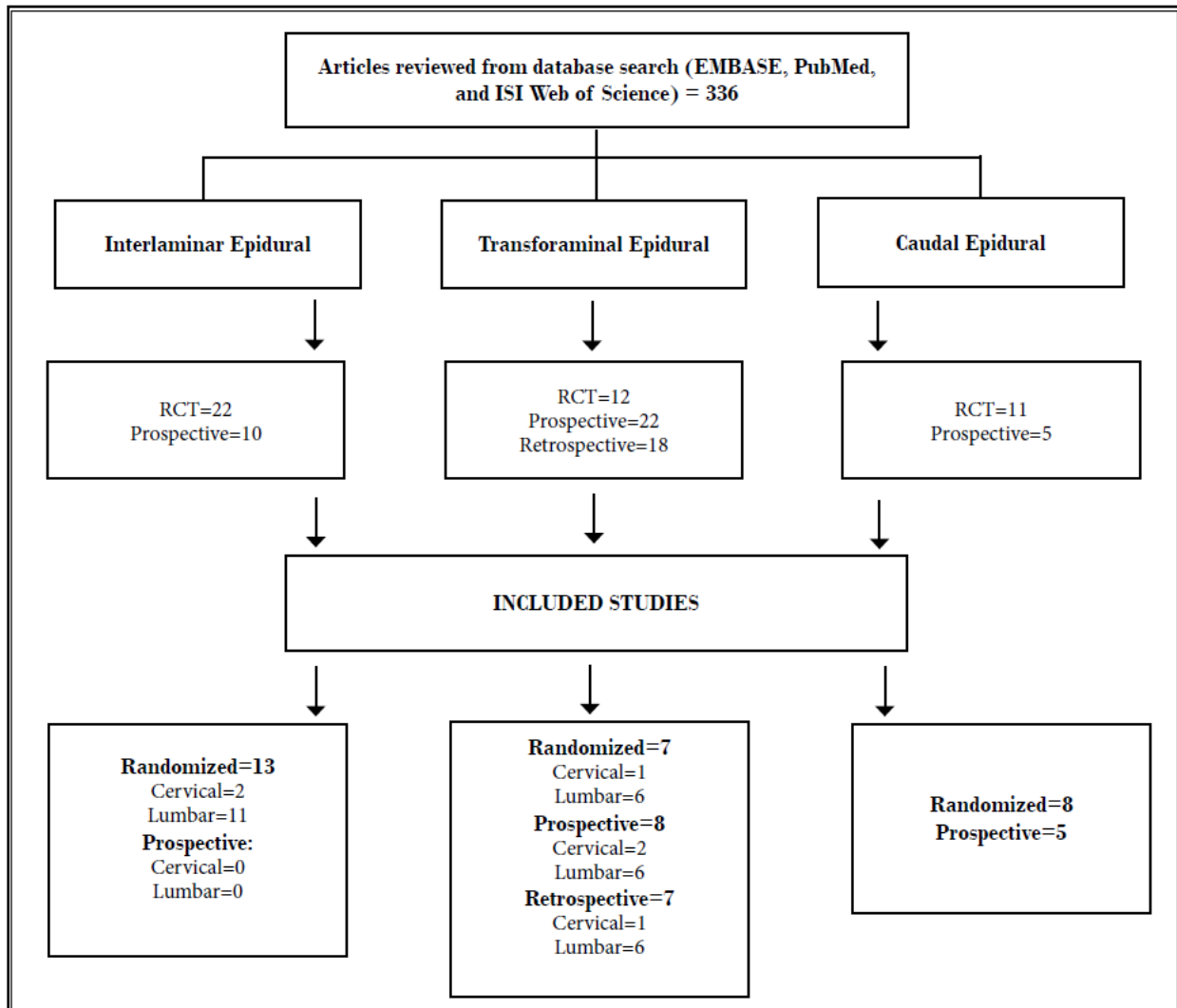
To discuss the risks of ESI, it is important to also consider the benefit of ESI in order to make a risk/benefit determination. Although corticosteroids are not FDA-approved for epidural injection, they are widely reported as providing symptomatic benefit for patients. As mentioned in the introduction, CDER has never approved an injectable corticosteroid product for administration via epidural injection. Therefore, the only available efficacy information is that reported in the published literature. Although such information may be useful for evaluating the efficacy of a particular product, there are a number of limitations of reports published in the medical literature that should be taken into consideration when weighing the value of the reported findings. These include:

1. Limited descriptions of the protocols that preclude a determination of whether subject selection bias, amendments to the protocol during the trial, and other methodological issues may have influenced the trial outcome.
2. Limited descriptions of the conduct of the trial that would allow an assessment of the validity of the findings based on protocol deviations.
3. Lack of original datasets that would allow verification of the statistical analyses and conclusions.
4. Limited ability to assure that the trial was conducted as reported and to verify that the data are legitimate.

Despite these potential shortcomings, it may be possible to draw reliable conclusions from the literature when multiple investigators from different institutions conduct similarly designed trials that produce similar results. For epidural corticosteroid injections, the results of numerous clinical trials have been reported in the literature; however, the findings are often mixed and comparisons are difficult to make due to differences in trial designs, e.g., corticosteroid(s) evaluated, pain syndrome evaluated, method of administration of study drugs, choice of comparator, endpoints studied, and duration of follow-up. As such, this overview will touch on systematic reviews or meta-analyses of randomized controlled trials that attempted to summarize the findings of groups of trials of ESI efficacy.

In 2007, Abdi et al. [9] performed a systematic review of the literature using Agency for Healthcare Research and Quality (AHRQ) criteria for the evaluation of randomized and non-randomized trials and the Cochrane Musculoskeletal Review Group's criteria for randomized trials to evaluate the efficacy of various types of epidural steroid injections (interlaminar, transforaminal, and caudal), in the management of various types of chronic pain (axial and radicular) in the neck and low back regions. The results of their literature search are summarized below in Figure 2.

Figure 2. Literature search results [Fig. 1 p. 188 from Abdi et al. [9]]



RCT – randomized, controlled trial

Using pain relief as the primary outcome measure and defining short-term improvement as lasting ≤ 6 weeks duration and long-term relief as lasting > 6 weeks duration, they reported the following results from their analyses of the “included studies.”

Table 2. Results from Abdi et al systematic review[9]

Type of Pain	Method of Injection	Level of Evidence for Short-Term Pain Relief	Level of Evidence for Long-Term Pain Relief
Cervical radiculopathy	Interlaminar	Moderate	Moderate
Cervical nerve root	Transforaminal	Moderate	Moderate

Type of Pain	Method of Injection	Level of Evidence for Short-Term Pain Relief	Level of Evidence for Long-Term Pain Relief
Lumbar nerve root	Transforaminal	Strong	Strong
Lumbar radicular	Lumbar interlaminar	Strong	Limited
Lumbar radicular	Lumbar transforaminal	Strong	Moderate
Lumbar radicular pain post lumbar laminectomy		Moderate	Moderate
Lumbar spinal stenosis	Transforaminal	Limited	Limited
Lumbar radiculopathy	Caudal epidural	Strong	Moderate
Post-lumbar laminectomy syndrome	Caudal epidural	Strong	Moderate

Based on these findings, the authors drew the following conclusions:

1. There is moderate evidence for interlaminar epidurals in the cervical spine and limited evidence in the lumbar spine for long-term relief.
2. The evidence for cervical and lumbar transforaminal epidural steroid injections is moderate for long-term improvement in managing nerve root pain.
3. The evidence for caudal epidural steroid injections is moderate for long-term relief in managing nerve root pain and chronic low back pain.

In 2008, Staal et al. [10] reported on a systematic review of the literature conducted with a focus on randomized, controlled trials, and then, in 2009, updated their search of the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE databases up to March 2007 for trials that were reported in English, French, German, Dutch, and Nordic languages [11]. Included in their analyses were studies on the effects of injection therapy involving epidural, facet, or local sites for subacute or chronic low back pain. Their search identified 18 trials involving 1,179 subjects. The injection sites included the epidural space, facet joints, and trigger points. All trials involved the use of corticosteroids, but the use of local anesthetics and other drugs with the corticosteroid was not a basis for exclusion. At the time of their initial review, they concluded that there was insufficient evidence to support the effectiveness of injection therapy; however, they noted that the heterogeneity of the studies may have limited the ability to draw definitive conclusions. To reduce heterogeneity in the updated review, the authors classified the studies first according to the target tissue of the injection, second according to the therapeutic agent that was used, and then, if possible, these strata were further subdivided into placebo-controlled trials and those that compared injections with other treatments. Furthermore, the authors excluded studies dealing specifically with the treatment

of radiculopathy, having assessed this use of epidural steroids in a previous review, which is also presented later in this document. The following criteria were used by the authors for inclusion into the review:

1. The treatment had to include injection therapy for pain relief.
2. Studies about injections into sacroiliac joints and studies in which the drugs were administered by means of a catheter and not directly by means of an injection were excluded.
3. The study had to have incorporated some outcome measure of pain. These outcomes were evaluated by the authors over both the short-term (≤ 6 weeks) and long-term (> 6 weeks).

The clinical relevance of the studies was assessed based on the following five questions and the extent to which they were addressed in a positive fashion:

1. Are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?
2. Are the interventions and treatment settings described well enough so that you can provide the same for your patients?
3. Were all clinically relevant outcomes measured and reported?
4. Is the size of the effect clinically important? (A 20% improvement in pain scores and a 10% improvement in functioning outcomes were considered by the authors to be clinically important.)
5. Are the likely treatment benefits worth the potential harms?

Their analyses, related to the use of epidural steroids, were divided into three categories: steroids versus placebo injections; steroid injections versus other treatments; and steroids combined with local anesthetics versus other treatments.

They found that there was limited evidence that epidural steroid injections were not significantly different from placebo injections in the short-term (based on a single trial involving 48 patients). There was moderate evidence for pain relief and limited evidence for work disability that epidural corticosteroid injections were not significantly different from placebo injections in the short term (based on one trial involving 35 patients).

Comparing epidural steroid injections to other treatments, there was limited evidence in the literature that the effects of epidural steroid injections were not significantly different from:

- NSAIDs for pain relief in the short term based on a single trial of 206 patients who were status post laminectomy[12];
- Intrathecal midazolam for pain relief and general improvement both in the short and intermediate term for 28 patients enrolled in a single trial[13]; and

- Epidural morphine, which was eventually combined with corticosteroids and administered epidurally, for pain relief in the short and intermediate term in a single trial involving 22 patients who were status post laminectomy[14].

Lastly, they noted that there was moderate evidence, based on two trials involving 56 patients, that there was no significant difference in the amount of analgesia provided between epidural steroid blocks with ropivacaine and epidural steroid blocks with bupivacaine.

Based on their analyses, the authors made the following three conclusions relevant to the current discussion:

1. There is limited evidence that epidural corticosteroid injections are no more effective than placebo injections for general improvement and work disability.
2. There is moderate evidence that epidural corticosteroid injections are no more effective than placebo injections for pain relief.
3. There is limited evidence that epidural corticosteroid injections are no more effective than other drug treatments for pain relief and general improvement.

In 2009, Roberts et al. [15] reviewed the literature evaluating the efficacy of lumbosacral transforaminal epidural steroid injections (TFESIs) in the treatment of radicular pain. Specifically, they searched MEDLINE, EMBASE, and the Cochrane database for the period between 1950 and May 2008. The authors restricted their review to those studies that were randomized controlled trials (RCTs), published in English, and which evaluated the efficacy of fluoroscopically guided TFESIs. The authors analyzed the studies utilizing a quality checklist modeled after the 2001 CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials. In all, they identified nine studies that included a majority of these items. Based on factors which included study design, inclusion criteria, symptom duration, randomization protocol, blinding protocol, intervention, control, outcomes, follow-up, dropout, and statistical analysis, each study was assigned a level of evidence: I (highest quality based on the randomized controlled design with either a significant difference between treatments or no significant difference but a narrow confidence interval) or II (high quality based on prospective cohort study or randomized controlled trial design and factors that detracted from the quality, e.g., low (80%) follow-up, low power, poor randomization technique, unblinded evaluators). The studies were also divided according to the control treatment. Lastly, the overall evidence was graded as A (good), B (fair), C (conflicting/poor quality), or I (insufficient). Five of the nine trials that were analyzed compared transforaminal epidural steroid injections to a control that permitted the efficacy of the steroid. The author's reviews of those trials are summarized Table 3 below.

Table 3. Efficacy evaluations of transforaminal epidural steroid injections (Table 4, pp. 662-662, from Roberts et al.[15])

Reference Year	Number of Patients Selection Criteria	Control	Intervention	Outcome Measures	Time of Measurements	Results	Strengths	Weaknesses	Level of Evidence
Vad et al.[16] 2002	48 patients; leg pain greater than back pain with symptoms > 6 wk, MRI with HNP with <50% intervertebral foraminal narrowing.	1-2 para-spinal saline trigger point injections (<i>n</i> = 23).	1-3 TFESIs with lidocaine and betamethasone (<i>n</i> = 25).	Roland-Morris score, visual numeric pain score, finger-to-floor distance, and a 0-4 patient satisfaction score.	Preinjection, 3 and 6 weeks and 3, 6, and 12 months post-injection.	Successful outcome if Roland-Morris score improved by 5 or more, pain reduced by greater than 50% and a patient satisfaction score of at least 2 at one year post-injection. 84% of intervention group and 48% of control group had a successful outcome, which is statistically significant.	Length of follow-up (1.4 y). Trigger point injection as a control.	Lack of blinding of patients and treating physicians. Raw data and baseline characteristics not given.	II
Devulder et al.[17] 1999	60 patients; history of spinal surgery for disk herniation with	TFI with bupivacaine and hyaluronidate	TFI with bupivacaine, hyaluronidate	Verbal rating score (0-4).	1, 3, 6 months post-injection.	There were no statistically significant differences	Uniform patient selection EMG and	Non-blinded study. Chronic	II

	EMG confirming chronic nerve pathology and imaging confirming nerve fibrosis.	dase	se ($n = 20$) vs. TFESI with bupivacaine , methylprednisolone ($n = 20$) vs. TFESI with bupivacaine , hyaluronidase, methylprednisolone ($n = 20$). Each group received 2 injections 1 week apart.			between groups. Overall, pain relief most prominent after 1 month, but decreased at 3 and 6 months.	imaging to determine chronic nerve pathology.	nerve pathology population cannot be generalized. Patient baseline characteristic not given.	
Riew et al.[18] 2000	55 patients; lumbar radicular pain with radiographic confirmation of nerve-root compression. Each patient considered a surgical	1-4 TFIs with bupivacaine ($n = 27$).	1-4 TFESIs with bupivacaine and betamethasone ($n = 28$).	Operative intervention .	13-28 months post-injection.	Significantly fewer patients in the intervention group (29%) pursued surgery, compared with the control group (67%).	Significant follow-up (13-28 months) . Patient and surgeon	Secondary outcome measures only obtained for non-operative group.	I

	candidate by the patient and the surgeon.						blinded to the intervention.		
Karppinen et al. [19] 2001	160 patients; leg pain greater than back pain for 3-28 weeks.	A single saline TFI (<i>n</i> = 80).	A single TFESI with Methylprednisolone and bupivacaine (<i>n</i> = 80).	Back and leg VAS, Oswestry, Nottingham Health Profile, physical exam, cost.	Immediately after the injection, 2 and 4 weeks post-injection and 3, 6, and 12 months post-injection.	Statistically significant results: immediately, leg pain decreased by 61% in treatment group compared with 44% in control group; at 2 weeks, improvement in all measures (except Schober) in both groups, with TFESI superior to control for leg pain, straight leg raise, Schober and patient satisfaction; at 3 months, controls had less back pain than TFESI;	Patients and physicians were blinded to the intervention. Large population size. Long follow-up.	Control group was not a true placebo. Patients were limited to only 1 injection.	I

						at 6 months, controls had less back pain and leg pain. At 1 y, there was no difference in outcome measures, but both groups improved.			
Ng et al.[20] 2005	86 patients; chronic unilateral radicular pain that failed conservative treatment.	A single TFESI with Bupivacaine only (n = 43).	A single TFESI with bupivacaine and methylprednisolone (n = 43).	Oswestry, VAS for back and radicular pain, change in walking distance, and patient's satisfaction level.	6 and 12 weeks post-injection.	Improvement in both groups for leg pain, Oswestry, and walking distance, but no statistically significant difference between the 2 groups. Only the duration of symptoms demonstrated a predictive response—the shorter the duration of symptoms, the better the	Patients and physicians were blinded to the intervention.	Duration of symptoms was greater in the treatment group compared with the controls. The control group is not a true placebo. Patients were limited to only 1	I

						response to the injection.		injection.	
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TFESI = transforaminal epidural steroid injections; MRI = magnetic resonance imaging; HNP = herniated nucleus pulposus; EMG = electromyogram; TFI = transforaminal injection; VAS = visual analog scale.

Based on their analysis, the authors conclude the following regarding the use of steroids when injected using a transforaminal approach to the epidural space:

- In patients with radicular pain secondary to herniated nucleus pulposus or spinal stenosis who are surgical candidates, TFESI is a surgery-sparing intervention compared with TFI of bupivacaine [11]. *Grade of Recommendation: A*
- In patients with sub-acute to chronic radicular symptoms, a single TFI of bupivacaine or saline alone has similar effects on both short-term and long-term pain and disability as a single TFESI [12,14]. *Grade of Recommendation: A*
- In patients with chronic nerve fibrosis and failed back surgery syndrome, pain relief is similar with a TFI of bupivacaine and hyaluronidase, a TFI of bupivacaine and methylprednisolone, and a TFI of bupivacaine, hyaluronidase, and methylprednisolone [10]. *Grade of Recommendation: B*

In 2012, Pinto et al [21] published their findings from a systematic review and meta-analysis of randomized, placebo-controlled trials assessing the efficacy of epidural corticosteroid injections in patients with sciatica. They searched the International Pharmaceutical Abstracts, PsycINFO, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and CINAHL over the period extending from the earliest records to April 27, 2012. The search strategy included keywords related to randomized, controlled trials; sciatica; and corticosteroids. In addition to the electronic searches, their team “hand-searched” the reference lists of eligible clinical trials and previous systematic reviews. The search was restricted to trials published in English.

Studies were eligible if they were randomized, controlled trials evaluating epidural corticosteroid injections compared with similar placebo interventions. Studies of the three anatomical approaches generally used for administering epidural corticosteroids, i.e., caudal, interlaminar, and transforaminal, were eligible. The authors considered “placebo” interventions as administration of an inert, i.e., no pharmacologic activity or innocuous substance (e.g., regular saline solution) either into the epidural space (to mimic epidural corticosteroid injection) or adjacent spinal tissue (e.g., subcutaneous, intramuscular, or interspinous). They also included clinical trials where a local anesthetic with a short duration of action was used in both the active treatment and control groups. To be eligible, clinical trials had to include only patients diagnosed with “sciatica,” or other pain conditions, e.g., nerve root compression or disc herniation, where the pain radiated below the knee.

Patients were classified as having acute (< 6 weeks), subacute (6 to 12 weeks), chronic (≥12 weeks), or mixed duration of symptoms. To enhance patient homogeneity, trials that reported the inclusion of patients who previously had surgery or patients with sciatica due to spinal canal stenosis were not included; however, trials that included patients with foraminal stenosis or lateral recess stenosis were considered eligible. Trials with mixed populations were eligible if the data for the subgroup of participants with sciatica could be clearly identified.

Eligible trials were required to report at least one of the following outcome measures:

- Overall pain intensity (when not specified as leg or back pain)
- Leg pain intensity
- Back pain intensity
- Disability status

The authors assessed trial methodological quality with the Physiotherapy Evidence Database scale. The data extracted from the trials included the mean differences and 95% Confidence Intervals (CIs) or means (final values or change in score), Standard Deviations (SDs), and sample sizes. When there was insufficient information in the trial reports, the authors took the additional steps of contacting the investigators or estimating the data using methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions. Lastly, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to evaluate the overall quality of the evidence using an adapted version of the criteria advocated by the Cochrane Back Review Group. Specifically, the GRADE classification was downgraded by 1 level for each of 4 factors considered:

- I. Design limitations (> 25% of participants from studies with low methodological quality [Physiotherapy Evidence Database score < 7 points])
- II. Inconsistent results (\leq 75% of participants from studies with findings in the same direction)
- III. Imprecision (< 300 participants for each outcome)
- IV. Reporting bias (a funnel plot showing evidence of small study effects)

Outcome data were extracted and grouped into 4 time points of assessment: immediate term (\leq 2 weeks after randomization), short term (> 2 weeks but \leq 3 months), intermediate term (> 3 months but < 12 months), and long term (\geq 12 months) follow-up evaluations. When several time points fell within the same category, the time point closest to 1 week for the immediate term, 8 weeks for the short term, 6 months for the intermediate term, and 12 months for the long-term was used. When more than one outcome measure was used to assess pain or disability, the outcome measure described as the primary outcome measure for the trials was included in the review. Scores for pain intensity and disability were converted to scales from 0 (no pain or disability) to 100 (worst possible pain or disability). Pain intensity measures used to calculate pooled effects were visual analog scale scores (range, 0 to 100) and numerical rating scale scores (range, 0 to 10); the disability measures pooled in the meta-analysis were Oswestry Disability Index scores (range, 0 to 100) and Roland–Morris Questionnaire scores (range, 0 to 24). The numerical rating scale and Roland–Morris Questionnaire scores were converted to the same 0-to-100 scale as in the visual analog scale and Oswestry Disability Index.

For the primary analysis, trials considered clinically homogeneous were grouped according to outcomes (pain and disability) and assessment time points (immediate term, short term, intermediate term, and long term). When trials presented more than one possible placebo-controlled intervention, the authors extracted data from the comparison group that they

thought most closely mimicked the epidural injection procedure and that they considered most likely to be inert. Pooled estimates were calculated using a random-effects model. For effect size calculation, overall pain was pooled together with leg pain based on the observation that leg pain is usually worse than back pain in patients with sciatica.

Secondary exploratory analyses included subgroup analyses to examine whether the short-term efficacy of epidural corticosteroid injections on leg pain varied by epidural injection approaches (caudal vs. interlaminar vs. transforaminal), type of placebo (epidural anesthetic vs. epidural saline vs. interspinous saline), and definition of sciatica (clinical assessment vs. required concordant imaging evidence). Pooled estimates for each subgroup were calculated using a random-effects model.

A total of 23 trials were ultimately included in the review. Epidurally administered corticosteroids investigated included methylprednisolone, prednisone or prednisolone, triamcinolone, and betamethasone. Thirteen of the trials evaluated the interlaminar approach for administration of the epidural steroids. The transforaminal and caudal approaches were investigated in 6 and 4 trials, respectively. The results for the meta-analysis of the weighted mean difference (WMD) for leg pain and disability or shown in the two figures below.

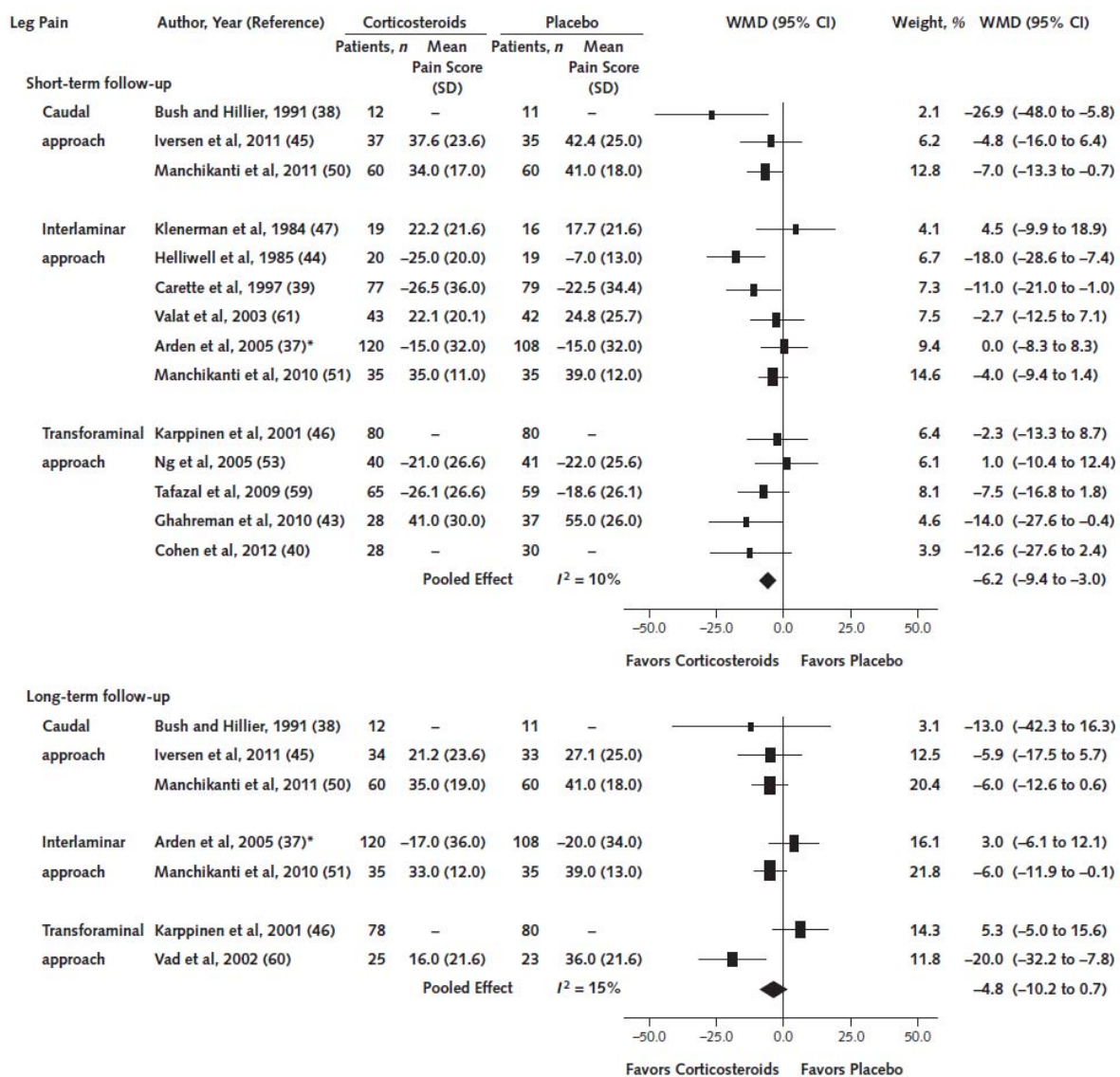
For short-term follow-up of leg pain, there were 14 trials involving 1,316 patients included in the analysis. Pooling showed a significant effect favoring epidural corticosteroids ($I^2 = 10\%$; mean difference, -6.2 [95% CI, -9.4 to -3.0]) on a scale from 0 to 100. For short-term follow-up of back pain, there were 6 trials involving 723 patients. The authors found that there was no short-term effect of epidural corticosteroid injections on this parameter ($I^2 = 0\%$; mean difference, 0.5 [CI, -3.9 to 4.8]). For disability, the authors pooled 10 trials involving 1,154 patients and found a significant effect of epidural corticosteroid injections compared with placebo ($I^2 = 0\%$; mean difference, -3.1 [CI, -5.0 to -1.2]). They determined that the overall quality of evidence for the short-term effect of epidural corticosteroid injections was the same for leg pain, back pain, and disability outcomes, which was high quality, according to the GRADE classification.

For long-term follow-up, leg pain, back pain, and disability showed similar non-significant results. A total of 7 trials involving 714 patients were pooled for the analysis of leg pain. The data failed to show long-term relief of leg pain when compared with placebo ($I^2 = 15\%$; mean difference, -4.8 [CI, -10.2 to 0.7]). For back pain, 3 trials involving 453 patients were pooled. For these, there was a non-significant effect ($I^2 = 0\%$; mean difference, 3.4 [CI, -2.4 to 9.2]). For disability, the authors were able to pool data from 6 trials involving 691 patients and found there was no difference between corticosteroids and placebo ($I^2 = 22\%$; mean difference, -2.7 [CI, -6.8 to 1.3]). The GRADE classification for the three components of the long-term analyses was rated as high quality.

In their discussion of the results, the authors stated that there is high-quality evidence showing that epidural corticosteroid injections have small, short-term effects on leg pain and disability

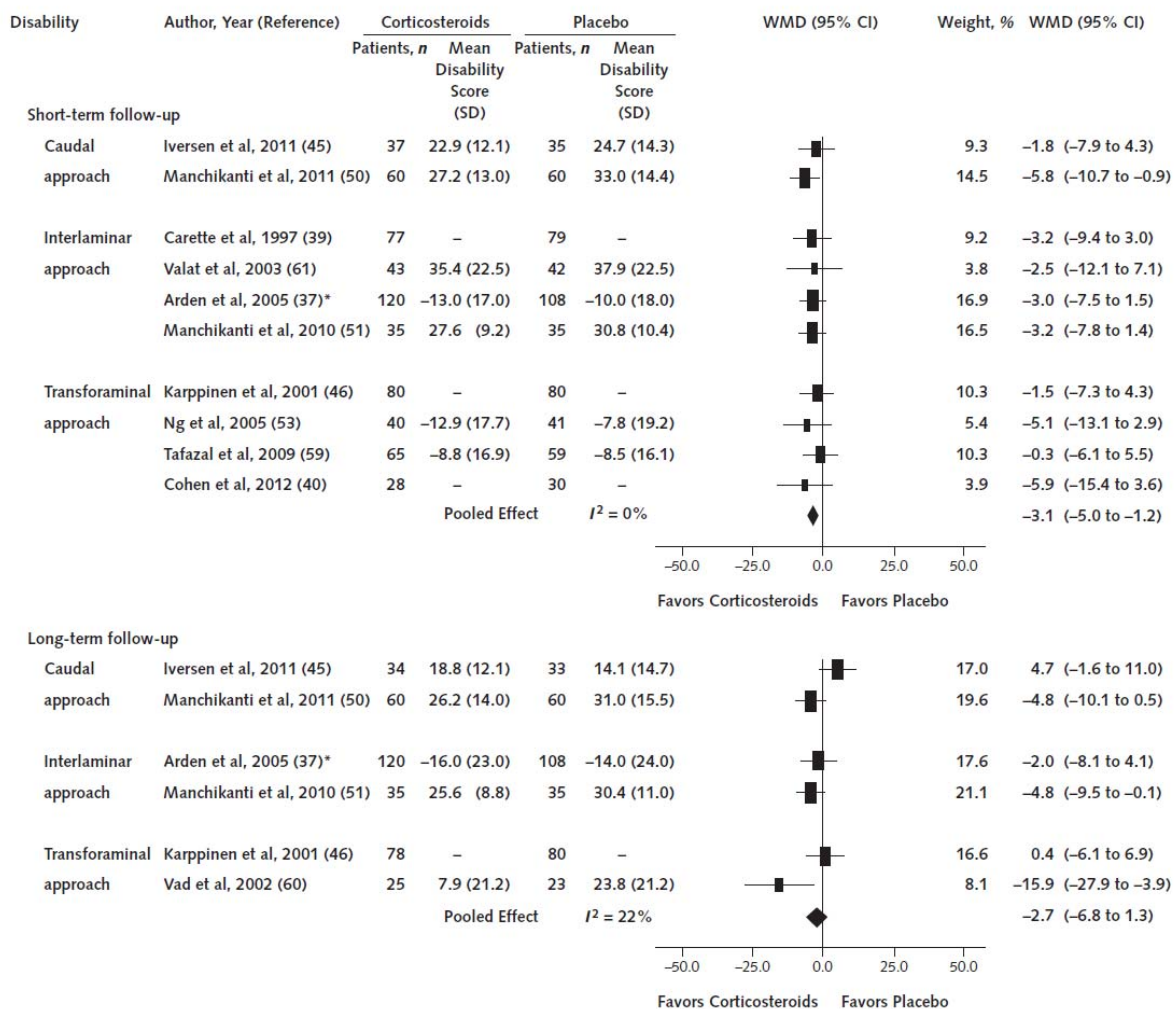
compared with placebo in patients with sciatica but no effect in the long term and no effect on back pain over either the short or long term. The small between-group effects of 6 and 3 points observed, respectively, for pain and disability (on a scale of 0 to 100) were considered insufficiently large to be judged clinically meaningful by either patients or clinicians.

Figure 3. Weighted Mean Difference for leg pain (Figure 2, p. 872, from Pinto et al.[21]). [Note that the reference citations are from the article and are not incorporated into this document.]



*Price et al. reported data from the same trial.

Figure 4. Weighted Mean Difference for disability (Figure 3, p. 873, from Pinto et al.[21]). [Note that the reference citations are from the article and are not incorporated into this document.]



*Price et al. reported data from the same trial.

In 2013, Cohen et al. [8] reported on their review of the literature in an effort to assess the efficacy of epidural steroid injections based on a number of factors including injection technique, region of the spine that was injected, dose and injectate administered, type of steroid, underlying pathology, and medical specialty of the investigators. Trials for their review were selected by searches of the PubMed, MEDLINE, EMBASE, and OVID databases from 1953 to February, 2013. Controlled trials, comparative-effectiveness studies, review articles, and case reports were all considered for inclusion, without language restrictions. In addition, the authors searched the reference lists of all articles for pertinent references that were missed during the initial screening.

Evidence was weighted using the Oxford Centre for Evidence Based Medicine consensus guidelines when relevant, and perceived bias. Levels of evidence cited in referenced systematic reviews were either based on US Preventive Services Task Force (USPSTF) criteria or, if classified by another scale, conveyed descriptively. For comparative effectiveness studies, i.e., type of epidural steroid injection [ESI] and type of corticosteroid, evidence of superiority was described using USPSTF levels of certainty. The authors identified 13 studies that met their inclusion criteria; their findings are summarized in Table 4 below.

Table 4. Summary of studies comparing transforaminal, interlaminar, and caudal epidural steroid injections (Table 3, pp 178-179, Cohen et al.[8])

Reference Year	Design	Subjects	Interventions	Results	Comments
Ackerman and Ahmad[22] 2007	Randomized evaluator-blinded	90 Patients with S1 radiculopathy from HNP	TF: 40 mg triamcinolone + 4 mL NS IL: 40 mg triamcinolone + 4 mL NS C: 40 mg triamcinolone + 19 mL NS	TF ESI > IL ESI or caudal ESI at 24 wk	Patients with ventral epidural spread, more common in TF ESI group, had better outcomes
Candido et al.[23] 2008	Randomized	60 Patients with unilateral radiculopathy from HNP and DDD	TF and IL: 80 mg methylprednisolone + 1 mL NS + 1 mL 1% lidocaine	No difference between TF ESI and IL ESI up to 6 mo	Study underpowered
Gharibo et al.[24] 2011	Randomized	42 Patients with unilateral radiculopathy from disk disease < 1 y	TF: 40 mg triamcinolone + 1 mL 0.25% bupivacaine IL: 80 mg triamcinolone + 2 mL 0.25% bupivacaine	TF ESI > IL ESI at 2-wk follow-up	Short follow-up period
Kolsi et al.[25] 2000	Randomized	30 Patients with sciatic or femoral neuralgia	TF and IL: 3.75 mg cortivazol + 2 mL 0.5% lidocaine	No difference between TF ESI and IL ESI up to 4 wk	TF ESI > IL ESI for initial mean pain score decrease
Kraemer et al.[26] 1997	Randomized	182 Patients with LBP	TF, IL, and paravertebral injections not described	TF ESI > IL ESI > paravertebral local anesthetic up to 3 mo	Intramuscular steroid injection added in saline group
Lee et al.[27]	Randomized	192 Patients with	TF: 20 mg triamcinolone	TF ESI > IL ESI	TF injections

Reference Year	Design	Subjects	Interventions	Results	Comments
2009	evaluator-blinded	axial LBP due to HNP or SS	+ 4 mL 0.5% lidocaine IL: 40 mg triamcinolone + 8 mL 0.5% lidocaine	up to 4 mo	received half IL ESI dose on each side. Differences between groups greater for SS patients
Rados et al.[28] 2011	Randomized	64 Patients with chronic unilateral lumbar radiculopathy	TF: 40 mg methylprednisolone + 3 mL 0.5% lidocaine IL: 80 mg methylprednisolone + 8 mL 0.5% lidocaine	No difference between TF ESI and IL ESI through 6 mo	TF ESI contained half the steroid dose and > 50% less LA
Thomas et al.[29] (2003)	Randomized	31 Patients with lumbosacral radiculopathy from HNP < 3 mo	TF and IL: 5 mg dexamethasone in 2-mL solution	TF ESI > IL ESI up to 6 mo	Fluoroscopy used for TF ESI, while IL ESI done blindly
Lee et al.[30] 2009	Retrospective	233 Patients with lumbosacral radiculopathy from SS or HNP TF	TF small volume: 40 mg triamcinolone + 2 mL 0.5% lidocaine TF large volume: 40 mg triamcinolone + 8 mL 0.5% lidocaine IL: 40 mg triamcinolone + 8 mL 0.5% lidocaine C: 40 mg triamcinolone + 15 mL 0.5% lidocaine	Satisfaction and pain scores: TF ESI and IL ESI > caudal ESI up to 2 mo Function: TF ESI > IL ESI > caudal ESI	Functional benefits of TF ESI more pronounced at 2 wk. Injectate volumes not standardized

Reference Year	Design	Subjects	Interventions	Results	Comments
Manchikanti et al. 1999	Retrospective case-control	225 Patients with LBP and leg pain	<p>TF: 1.5-3 mg betamethasone + 1 mL 1% lidocaine</p> <p>IL: 120 mg depo-methylprednisolone + 10 mL 0.5% lidocaine, with 80 mg methylprednisolone on subsequent injections</p> <p>C: 80 mg depo-methylprednisolone + 1Y mL 0.5% lidocaine</p>	TF ESI and caudal ESI 9 IL ESI at 1- to 3-mo follow-up, but no difference between groups at 3- to 6- and 6- to 12-mo follow-up	Longer pain duration in caudal ESI group. Variable steroid dose in TF ESI and variable follow-up period
Schaufele et al.[31] 2006	Retrospective case-control	40 Patients with lumbosacral radiculopathy from single-level HNP	<p>TF: 80 mg methylprednisolone + 1-2 mL 2% lidocaine</p> <p>IL: 80 mg methylprednisolone + 2-3 mL 1% lidocaine</p>	TF ESI > IL ESI; variable follow-up period averaging 3 wk	Higher baseline pain scores in IL ESI group. Short follow-up period

Reference Year	Design	Subjects	Interventions	Results	Comments
Smith et al.[32] 2010	Retrospective case-control	38 Patients with lumbosacral radiculopathy from SS	TF: 80 mg methylprednisolone + 1-2 mL 2% lidocaine IL: 80 mg methylprednisolone + 2Y3 mL 2% lidocaine	No difference between TF ESI and IL ESI; variable follow-up averaging 4-6 wk	Study underpowered
Mendoza-Lattes et al.[33] 2009	Retrospective case-control	93 Patients with mostly lower lumbar radiculopathy	Caudal: up to 3 injections of 2 ml of 40 mg/mL depo-methylprednisolone or 3 ml of 6 mg/mL betamethasone Transforaminal: up to 3 injections of a 1:1 solution containing 1.5-2 mL of bupivacaine 0.25% mixed with depo-methylprednisolone or betamethasone	C = TF through 2-y follow-up	16 Patients lost to follow-up. Equivalent rates of surgery between groups. Low volumes used for caudal injections. Included some patients with stenosis and spondylolisthesis

C indicates caudal; LA, local anesthetic; SS, spinal stenosis; DDD, degenerative disk disease.

Based on the findings, the authors concluded that a majority of the studies support the superiority of transforaminal ESI to IL or caudal ESI. Transforaminal ESI was superior to IL ESI or caudal in 5 of 8 randomized controlled trials comparing the two routes, and 3 of 5 retrospective studies. Of the two studies failing to show superiority of the TF approach, according to the authors, one was underpowered and used a variation on the classic IL approach; the other trended in the direction favoring TFESIs.

The authors also noted what they considered to be paradoxical phenomenon in that their review of randomized clinical trials found that a higher proportion of controlled studies evaluating caudal ESIs were positive than those evaluating IL ESIs

The authors also searched the literature for studies comparing the efficacy of ESI based on the type of steroid used. They were able to identify six studies; three of which were randomized, and three of which were retrospective. The authors summarized the findings from these studies as indicated in Table 5 below.

Table 5. Summary of studies comparing the efficacy of different steroids used in epidural steroid injections (from Table 4, p. 182, Cohen et al.[8])

Reference Year	Design	Subjects	Interventions	Results
Dreyfuss et al.[34] 2006	Randomized	30 Patients with unilateral cervical radiculopathy	TF ESI with 0.75Y1 mL 4% lidocaine + either: A: Dexamethasone 12.5 mg B: Triamcinolone 60 mg	Nonsignificant trend favoring particulate steroid
Lee et al.[35] 2009	Retrospective	159 Patients with cervical radiculopathy who failed IL ESI or had previous surgery	TF ESI with either: A: Dexamethasone 10 mg B: Triamcinolone 40 mg	Nonsignificant trend favoring particulate steroid
Kim and Brown[36] 2011	Randomized Single-blind	60 Patients with lumbar radiculopathy ≥ 6 mo	IL ESI with 10 mL consisting of 2 mL 0.25% bupivacaine + NS + either: A: Dexamethasone 15 mg B: Methylprednisolone 80 mg	Nonsignificant trend favoring particulate steroid
Park et al.[37] 2010	Randomized	106 Patients with lumbar radiculopathy	TF ESI with 1 mL 1% lidocaine + either: A: Dexamethasone 7.5 mg B: Triamcinolone 40 mg	Particulate > nonparticulate steroid for pain reduction
Noe and	Retrospective	52 Patients with LBP referred for	IL ESI with either: A: Betamethasone 15 mg	Particulate > nonparticulate

Reference Year	Design	Subjects	Interventions	Results
Haynsworth[38] 2003		ESI	B: Methylprednisolone 80 mg	steroid for pain reduction, improvement in disability
Shakir et al.[39] 2013	Retrospective	441 Patients with cervical radiculopathy	TF ESI with 1 mL of 1% lidocaine + either: A: Dexamethasone 15 mg B: Triamcinolone 40 mg	No difference in pain score reduction between groups

The authors considered these data, i.e., those evaluating the different types of steroids used in ESIs, to be mostly limited to underpowered randomized or retrospective studies comparing “particulate” to “nonparticulate” corticosteroids. Of the three randomized studies, two reported a non-significant benefit in favor of the “particulate” steroid group, whereas the largest trial, with 106 subjects, reported a statistically significant difference between treatments favoring “particulate” steroids. In the 3 retrospective studies, one found “particulate” steroids to be significantly better than the “nonparticulate” comparator; one showed a trend toward superiority for “nonparticulate” steroids in patients with cervical radiculopathy; and the third study found no difference between the two classes of steroids for cervical TF ESI. Thus, the authors concluded that there was evidence, albeit with a low degree of certainty, that “particulate” steroids provide superior relief compared to “nonparticulate” steroids.

In 2014, Jamison et al. [40] reported the results of their evidence-based review of the literature related to the use of epidural injections for the lysis of adhesions (LOA) in the treatment of pain related to spinal stenosis and for radicular pain related to herniated discs. They noted that spinal stenosis may result from multiple causes including hypertrophy of the facet joints or ligamentum flavum, spondylolisthesis, intervertebral disc herniation, and congenitally short pedicles. They further noted that, in the absence of surgery, the causes of adhesions are not well understood, but they occur in the presence of inflammatory processes. Because the causal relationship between adhesions and pain has not been clearly established, the mechanism(s) of action by which epidural injections may provide relief is less certain, e.g., disruption of adhesions, dilution of inflammatory mediator, better spread of medication to the site from which the pain emanates.

Articles included in the review were selected from searches of PubMed, Medline and EMBASE databases from 1970 through 2013. The authors used the search terms "epidural lysis of adhesions," "lysis of adhesions," "epidural neuroplasty," "epidural adhesions," "epidural scar tissue," "chronic pain," and "pain epidemiology." Controlled trials, comparative-effectiveness studies, review articles, and case reports were all considered for inclusion without language restrictions. The authors took the additional step of searching the reference lists of all articles for pertinent references that were missed during the initial screening. They found that the body of literature pertaining to epidural lysis of adhesions contained several systematic reviews and a relatively small number of randomized studies from a select group of investigators. Evidence of benefit in the settings of spinal stenosis and failed back surgeries were generally positive with ratings ranging from fair to strong. The randomized studies that were frequently cited were summarized by the authors in tabular form which is reproduced in Table 6 below with those studies that permit an assessment of the effects of epidural steroids highlighted in gray.

Table 6. Randomized studies analyzed by Jamison et al (Table 1, p. 68 from Jameson et al. [40])

Reference Year	Design	Subjects	Interventions	Results	Comments
Spinal Stenosis					
Manchikanti et al.[41] 2009	Randomized	50 patients with radicular pain and central spinal stenosis	I. control/caudal injection and normal saline II. LOA with hypertonic saline Both groups received epidural steroid and local anesthetic	<ul style="list-style-type: none"> Superior pain relief at 3, 6 and 12 months in Group II 76% of Group II had significant pain relief at 12 months compared to 4% in Group I 	<ul style="list-style-type: none"> Only 25 patients per intervention Unclear effect of targeted steroid in Group II
Failed Back Surgery					
Manchikami et al.[42] 2009	Randomized	120 patients h/o lumbar surgery and low-back pain	I. control/caudal injection and normal saline II. LOA with hypertonic saline Both groups received epidural steroid and local anesthetic	<ul style="list-style-type: none"> Superior pain relief at 3, 6 and 12 months in Group II 73% of Group II had significant pain relief at 12 months compared to 12% in Group I 	<ul style="list-style-type: none"> More repeat procedures in Group II Unclear effect of targeted steroid in Group II
Yousef et al.[43] 2010	Randomized, double-blind	38 patients h/o lumbar surgery and low-back pain	I. caudal II. caudal with hyaluronidase Both groups received steroid, 10 mL of local anesthetic and 30 mL of hypertonic saline	<ul style="list-style-type: none"> Superior pain relief in Group II at 6 and 12 months, also decreased opioid intake 	<ul style="list-style-type: none"> Catheter was not used Small sample size
Kim et al.[44] 2012	Randomized	60 patients h/o lumbar surgery and low-back pain with	I. Steroid and local anesthetic II. Hyaluronidase and local anesthetic	<ul style="list-style-type: none"> Percentage of patients reporting significant relief at 12 weeks greatest 	<ul style="list-style-type: none"> Short follow-up Catheter not used

Reference Year	Design	Subjects	Interventions	Results	Comments
		radiculopathy	III. Steroid, hyaluronidase and local anesthetic All medications via interlaminar injection	in group III (52.2% compared to 0% in Groups I and II)	
Chun-jing et al.[45] 2012	Randomized, double-blind	92 patients h/o lumbar surgery and radicular pain	I. Control/epidural steroid II. LOA with 50-80 mL saline, steroid	VAS in Group II significantly improved at 6 months	<ul style="list-style-type: none"> Group I intervention not well-described Type of saline not described
Radiculopathy					
Heavner et al.[46] 1999	Randomized	81 patients with radiculopathy and low-back pain	I. Hypertonic saline plus hyaluronidase II. Hypertonic saline III. Normal saline IV. Normal saline plus hyaluronidase All groups received steroid and local anesthetic	<ul style="list-style-type: none"> Similar results in all four groups with overall 80-88% improvement at discharge, 25-69% at 12 months Non-significant trend of hypertonic patients requiring less repeat procedures 	<ul style="list-style-type: none"> No control group 24 patients dropped out
Manchikanti et al.[47] 2004	Randomized, double-blind	75 patients with low-back pain and/or radiculopathy	I. Control/caudal injection II. Normal saline III. Hypertonic saline All groups received epidural steroid and local anesthetic	<ul style="list-style-type: none"> Significant improvement in Groups II and III at all time periods, but better relief with hypertonic saline: 72% had at least 50% improvement at 12 mo compared to 	<ul style="list-style-type: none"> Unclear when additional procedures were performed in relation to data collection

Reference Year	Design	Subjects	Interventions	Results	Comments
				60% in Group II	
Veihelmann et al.[48] 2006	Randomized	99 patients with radiculopathy and low-back pain	I. Physical therapy II. LOA with hypertonic saline	<ul style="list-style-type: none"> Significant improvement in VAS and ODI in Group II at 3 months 	<ul style="list-style-type: none"> Unable to assess data for 6 and 12 month follow-up Type and frequency of PT unclear
Kim et al. [44] 2011	Randomized	61patients with low-back pain and radiculopathy	I. Steroid and local anesthetic II. Hyaluronidase and local anesthetic III. Steroid, hyaluronidase and local anesthetic All medication via interlaminar injection	<ul style="list-style-type: none"> Percentage of patients reporting significant relief at 8 weeks greatest in group III (70.4% compared to 31.3% in Group II, 44.4% in Group I) 	<ul style="list-style-type: none"> Short follow-up Catheter was not used Started with 101 patients, 40 patients excluded from final analysis
Gerdesmeyer et al (2013). [49]	Randomized, double-blind	90 patients with radiculopathy	I. Placebo (subcutaneous catheter) II. LOA with local anesthetic, steroid, hypertonic saline and hyaluronidase Both groups had physical therapy	93% of Group II had at least 50% pain relief at 12 months compared to 69% in Group I	<ul style="list-style-type: none"> Three-day protocol used Significant placebo effect

There were only three randomized trials that included treatment arms which allowed some assessment of the efficacy of steroids administered in the epidural space. These trials involved patients with radicular pain associated with the lumbar spine. Coadministration of the steroids with other agents, e.g., local anesthetics, hyaluronidase, and saline, limit the ability to fully discern the magnitude of the effect steroids had in the pain relief observed. With no controlled studies evaluating the role of cervical LOA for the treatment of spinal stenosis and disc herniation, it is not possible to evaluate the possible role of epidural steroids in the related pain syndromes. The authors drew the following conclusions relevant to the use of epidural steroids in the treatment of pain associated with adhesions:

1. There is weak positive evidence that LOA is more effective than conventional caudal epidural steroid injections for failed back surgery syndrome and spinal stenosis, and that LOA is more effective than sham adhesiolysis and conservative management for lumbosacral radiculopathy.
2. Factors that may contribute to the enhanced efficacy compared to traditional epidural steroid administration include the high volume administered, the use of hypertonic saline, and to a lesser extent the use of hyaluronidase and a navigable catheter to mechanically disrupt scar tissue and guide medication administration.

In 2014, Chang-Chien and colleagues [50] published the findings of their systematic review of studies reported in the literature that compared the efficacy of transforaminal epidural steroid injections (TFESI) to interlaminar epidural steroid injections (ILESI) for treating unilateral lumbosacral radicular pain (LSRP). The authors used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines as the standards for conducting the review. The primary studies for analysis were controlled trials in which patients were randomized to TFESI or ILESI. Non-randomized studies were to be considered as part of a secondary review, if only a small number of randomized controlled trials were found. The authors excluded studies that had poorly described needle placement methodology, did not use fluoroscopic guidance for needle placement, did not report standardized pain scores at defined follow-up intervals, or did not provide statistical analyses of the results.

Their literature search utilized Medline (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus databases. These were searched for relevant English language publications from 1966 through August, 2013. The Cochrane Risk of Bias Tool was utilized to assess for bias in the identified prospective studies. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the identified non-randomized trials. The United States Preventive Services Task Force (USPSTF) level of evidence classification was used to grade the level of evidence for each of the studies.

The authors analyzed the available data by comparing differences in age, pain, and functional improvement between TFESI and ILESI using independent samples t-test; differences in gender, level of injection, or type of corticosteroids between the two groups were analyzed by χ^2 test. Forest plots and I^2 calculation were performed for comparing pain and functional improvements following the treatments.

The authors identified eight studies that satisfied the criteria for inclusion in their analyses. They noted that some of the studies included caudal epidural steroid injection as part of their research protocol. For these studies, only the data from TFESI or ILESI were included for analysis. Table summarizes the findings for the eight studies.

Table 7. Summary of studies comparing transforaminal and interlaminar approaches to epidural steroid injections (Table 8, p. E517, from Chang-Chien et al. [50])

Reference Year	Study Type	Cause of Lumbar Radicular Pain	TFESI	ILESI	Duration of Follow- Up	Pain Improvement TFESI vs. ILESI	Functional Improvement TFESI vs. ILESI
Gharibo et al.[51] 2011	Prospective Randomized Blinded (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 20 40 mg triamcinolone + 1 mL 0.25% bupivacaine At 2 levels	n = 18 80 mg triamcinolone + 2 mL 0.25% bupivacaine Vol: 4mL	10-16 days	73.4% vs. 44.3%	43.6% vs. 49.3%
Candido et al.[52] 2008	Prospective Randomized Single-Blinded (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 28 80 mg MPA + 1 mL 1% lidocaine + 1 mL NSS	n = 29 80 mg MPA + 1 mL 1% lidocaine + 1 mL NSS	1 month 6 months	16.5% vs. 23.1% 25.5% vs. 39.2%	N/A N/A
Rados et al.[52] 2011	Prospective Randomized (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 32 40 mg MPA + 3 mL 0.5% lidocaine	n = 32 80 mg MPA + 8 mL 0.5% lidocaine	24 weeks	45.6% vs. 43.5%	28.3% vs. 25%
Ackerman and Ahmad[52] 2007	Prospective Randomized Blinded (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 30 40 mg triamcinolone + 4 mL NSS	n = 30 40 mg triamcinolone + 4 mL NSS	2 weeks 24 weeks	72.1% vs. 35.2% N/A	53.3% vs. 60.6% N/A
Kolsi et al.[53] 2000	Prospective Randomized Double- Blinded	Lumbar Disc Herniation and/or	n = 17 3.75 mg Cotivazol Vol:	n = 13 3.75 mg Cotivazol Vol:	28 days	62.8% vs. 63.5%	34.8% vs. 50.9%

Reference Year	Study Type	Cause of Lumbar Radicular Pain	TFESI	ILESI	Duration of Follow- Up	Pain Improvement TFESI vs. ILESI	Functional Improvement TFESI vs. ILESI
Smith et al.[54] 2010	Retrospective Case-control (Level II-3)	Spinal Stenosis	n = 19 80 mg MPA + 1-2 mL 2% lidocaine Vol: 3-4 mL	n = 19 80 mg MPA + 2-3 mL 1% lidocaine Vol: 4-5 mL	4- 6 weeks	30.5% vs. 39.5%	N/A
Lee et al.[30] 2009	Retrospective Case-control (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 115 40 mg triamcinolone + 2 or 8 mL 0.5% lidocaine Vol: 3 or 9 mL	n = 64 40 mg triamcinolone + 8 mL 0.5% lidocaine Vol: 9 mL	1 month 2 months	78.0% v. 64.5% 68.2% vs. 51.6%	N/A N/A
Schaufele et al.[55] 2006	Retrospective Case-control (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 20 80 mg MPA + 1-2 mL 2% lidocaine Vol: 3-4 mL	n = 20 80 mg MPA + 2-3 mL 1% lidocaine Vol: 4-5 mL	2-3 weeks	45.8% vs. 19.2%	N/A

The authors noted that there were important caveats and limitations that need to be considered when evaluating their findings. These included:

1. There was a lack of consistency between the studies cited for inclusion and exclusion criteria.
2. There was a lack of consistency or standardization of doses, injectate volumes or types of glucocorticoids utilized for either TFESI or ILESI between studies, or even between the different approaches used in the same study.
3. There was a lack of standardization of follow-up periods or for the number or the type of interval treatments, including additional injections, performed in either group.
4. No consensus was identified between the need for the addition or lack of the addition of local anesthetic to the steroid, or to the type of local anesthetic or dose used, which was disparate in all studies.
5. A standardized approach to the interlaminar space for ILESI and to the intervertebral foramen during TFESI was absent.
6. Needle type, gauge, and rate of injection varied among studies.
7. Statistical methodologies were applied in a disparate manner in many of the studies which met inclusion criteria.

Based on these findings, the authors concluded that, “based on the 5 randomized, controlled trials consisting of 249 subjects which directly compared TFESI to ILESI for unilateral lumbosacral pain secondary to disc herniation/degeneration, there is high quality evidence to support a finding of no clinically significant difference in efficacy for pain relief or functional improvement between the 2 techniques at all follow-up “intervals.”

In summary, there are numerous clinical trials reported in the literature that have assessed the efficacy of epidural steroid injections for the treatment of pain related to the spine. As indicated by the systematic reviews described above, it is, at best, difficult to utilize the available data to consistently demonstrate the efficacy of this use of corticosteroids. How best to evaluate the benefit of ESI in the face of the multiple and heterogeneous factors associated with the injections themselves and evaluations of pain relief that follow the injections will be a topic of the Advisory Committee panel discussion at the meeting.

5 Summary of Division of Pharmacovigilance Review of Cases from FDA's Adverse Event Reporting System and the Medical Literature

The Division of Pharmacovigilance II (DPV) evaluated cases identified in the FDA Adverse Event Reporting System (FAERS) database and reviewed the published medical literature for an association between serious neurologic adverse events and the use of epidural steroid injections (ESIs). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that DPV provide an up-to-date assessment of the FAERS data and the medical literature which describe ESIs and catastrophic neurologic events and also provide an assessment of a potential association of arachnoiditis with injectable corticosteroids.

DPV's analysis of the FAERS cases (including 18 published case reports) and the medical literature suggests an association between the use of ESIs and serious neurologic adverse events (see Attachment D). DPV identified 131 FAERS cases of serious neurologic adverse events, including 41 cases of arachnoiditis. Serious neurologic adverse events in addition to arachnoiditis include paraparesis/paraplegia, quadriplegia, spinal cord infarction, stroke, thrombosis/thromboembolism, sensory disturbances, nerve injury, blindness, seizures, bowel/bladder dysfunction, and psychological/behavioral changes. The FAERS data and the medical literature suggest that use of imaging does not eradicate the risk of serious neurologic outcomes.

Medical organizations and other groups outside of FDA often refer to injectable steroids as either "particulate" (methylprednisolone acetate, triamcinolone acetonide or hexacetonide,, betamethasone acetate, betamethasone acetate/betamethasone sodium phosphate) or "non-particulate" (dexamethasone sodium phosphate, betamethasone sodium phosphate, methylprednisolone sodium succinate, hydrocortisone sodium succinate). For the purpose of the review, DPV considered the suspensions to be "particulates" and the solutions to be "non-particulates". Serious neurologic adverse events were reported with both types of preparations. The case series generated for this review contains many more reports for "particulate" steroids (n = 116) compared with "non-particulate" steroids (n= 4). Eleven cases did not report a formulation. It is not known whether this difference reflects greater utilization of "particulate" steroids or greater toxicity. All five of the cases reporting a fatal outcome among the case series reported the use of "particulate" steroids, although the cause of death in two cases (both reporting arachnoiditis) was due to completed suicide.

The published medical literature is extensive, although much of it focuses on efficacy. It is acknowledged by virtually all authors that serious neurologic events can occur in association with epidural steroid injections. Although there is no generally agreed upon estimate of frequency, these events are generally considered to be rare. Despite the fact that there are published cases of serious neurologic events in diverse settings, there is a general consensus that transforaminal injections are less safe than interlaminar or caudal injections; that "particulate" steroids can lead to embolic events if injected intravascularly whereas "non-

particulates” will not; and imaging to confirm appropriate needle placement prior to injection is of value. However, there are no large scientific studies that support a single approach or formulation as being safer than another.

The 41 cases of arachnoiditis reported with ESI use did not provide sufficient clinical detail to make a reasonable assessment regarding causality. The majority of reports were submitted by consumers (n=37) and 39 cases reported “particulate” corticosteroid injection. Only one case reported a route (interlaminar) and seven cases reported the injection site (1 cervical, 4 lumbar, 1 lumbar/sacral, 1 sacral).

In summary, serious or catastrophic neurologic events following ESI are reported in a broad range of settings, and no single mode of administration has been identified as free of risk with any degree of certainty. Most cases reported administration of a “particulate” steroid and there was an imbalance seen for transforaminal injections, compared with the interlaminar or caudal routes. However, any implication for differential risk is limited due to lack of reliable information about utilization of different formulations or routes of administration.

It is important to note that FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

See Attachment 2 for the full review. Attachments 3, 4, and 5 are previous reviews of this topic.

6 Relevant Pre-clinical Data

There are two publications regarding corticosteroid injection in animal models that may provide some useful information. The articles are summarized briefly here.

- Okubadejo et al.[56] in a small pilot study with male pigs compared the effects on the CNS of the intra-arterial passage of particulate methylprednisolone acetate versus soluble dexamethasone sodium phosphate or prednisolone sodium succinate. The study found that all pigs that received particulate methylprednisolone had serious neurologic sequelae (eosinophilic neuronal necrosis involving midbrain, brainstem, and temporo-occipital lobe) and required ventilatory support. None of the animals that received soluble dexamethasone or prednisolone had noticeable deficits. There appeared to be a strong relationship between the presence of particulate steroids and the observed CNS findings; however, the study was small (2 to 4 animals per treatment group) and lacked appropriate vehicle-control groups.
- Dawley et al.[57] conducted a prospective in vivo study in Wistar rats to examine whether intravascular injection of particulate and non-particulate steroids leads to microembolization. Five steroid products were tested: Depo-Medrol (listed as particulate formulation), Depo-Medrol carrier, Solu-Medrol (listed as non-particulate formulation), Decadron and normal saline. Neurological deficits were observed in the Depo-Medrol (N= 4/11) and Solu-Medrol groups (N= 1/8) but not the other treated groups. Brain lesions were observed in these animals. Cerebral hemorrhage was observed in Depo-Medrol (N=11), Depo-Medrol carrier (N=6), Solu-Medrol (N= 6) treated animals. Hemorrhagic lesions were observed as follows: Depo-Medrol (N=8/11), Depo-Medrol carrier (N=3/6), Solu-Medrol (N= 8/8), Decadron (N=0/5) and normal saline (N=0/6). Evans Blue leakage was observed in animals treated with Depo-Medrol and Solu-Medrol at approximately 2 hours post treatment but not saline, suggesting that these drug formulations damaged the brain tissue to compromise the blood-brain-barrier. Decadron did not induce injury under the study conditions.

Based on these data, both particulate and non-particulate steroids can induce CNS injury. There were some limitations in this study as it relates to the current human CNS effects. First, this study did not evaluate the same route of administration as that where the clinical CNS toxicities were observed, the sample size for each group was small and variable in the study report, and similar toxicities were not observed in these animals as those observed in the clinic (no clinical observations, no deaths, no seizures) despite significant brain damage after three days post-treatment.

7 Estimates of the Frequency of Epidural Steroid Injections (ESI)

To assess the potential impact of regulatory actions on the conduct of ESI, FDA sought to estimate the frequency of ESI in the U.S. population. Since there is no national database in which to identify patients undergoing medical procedures, it was decided to examine electronic healthcare data available to the Agency for several subpopulations in the U.S. These included Centers for Medicare and Medicaid Services (CMS or Medicare) data, which provides close to a census on health care for those over the age of 65 years, as well as Mini-Sentinel data which can provide characteristics of recipients of ESI in younger populations, despite the fact that the counts of patients are not nationally projected. Further description of these data sources is provided below.

Following discussions with FDA's internal subject matter experts, a decision was made for both data sources to use the HCPCS codes listed in Table 8 for our definition of epidural steroid injections in electronic healthcare data. The last four codes in the table were used to define the subset of transforaminal ESI.

Table 8. CPT codes for epidural injection used in the Medicare and Mini-Sentinel queries

Current Procedural Terminology (CPT) codes indicating epidural injection	
62289	Injection other than anesthetic, antispasmodic, contrast, or neurolytic solutions; lumbar or caudal epidural
62310	Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, includes contrast for localization when performed, epidural or subarachnoid; cervical or thoracic
62311	Injection(s), of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, including needle or catheter placement, includes contrast for localization when performed, epidural or subarachnoid; lumbar or sacral (caudal)
62318	Injection(s), including indwelling catheter placement, continuous infusion or intermittent bolus, of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, includes contrast for localization when performed, epidural or subarachnoid; cervical or thoracic
62319	Injection(s), including indwelling catheter placement, continuous infusion or intermittent bolus, of diagnostic or therapeutic substance(s) (including anesthetic, antispasmodic, opioid, steroid, other solution), not including neurolytic substances, includes contrast for localization when performed, epidural or subarachnoid; lumbar or sacral (caudal)
64479	Cervical/Thoracic transforaminal epidural injections;
64480	Cervical/Thoracic transforaminal epidural injections add-on
64483	Lumbar/sacral transforaminal epidural injections
64484	Lumbar/sacral transforaminal epidural injections add-on

Table 9 below lists the HCPCS “J-codes” that were used to identify the corticosteroid injection.

Table 9. CPT codes for epidural injection used in the Medicare and Mini-Sentinel queries

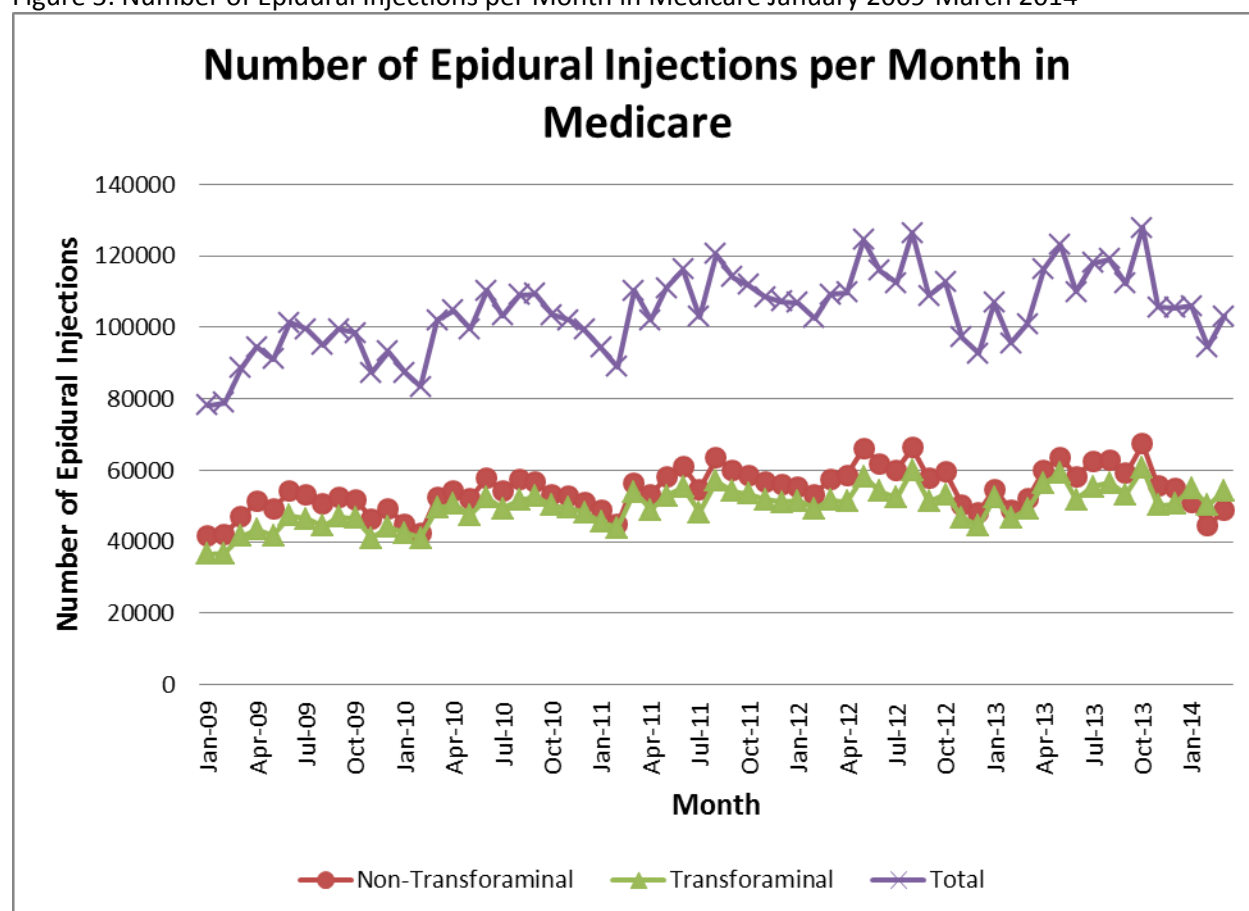
Code	Description of Procedure
J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg
J0704	Injection, betamethasone sodium phosphate, per 4 mg
J1020	Injection, methylprednisolone acetate, 20 mg
J1030	Injection, methylprednisolone acetate, 40 mg
J1040	Injection, methylprednisolone acetate, 80 mg
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J1700	Injection, hydrocortisone acetate, up to 25 mg
J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
J2640	Injection, prednisolone sodium phosphate, to 20 mg
J2650	Injection, prednisolone acetate, up to 1 ml
J2920	Injection, methylprednisolone sodium succinate, up to 40 mg
J2930	Injection, methylprednisolone sodium succinate, up to 125 mg
J3300	Injection, triamcinolone acetonide, preservative free, 1 mg
J3301	Injection, triamcinolone acetonide, not otherwise specified, 10 mg
J3302	Injection, triamcinolone diacetate, per 5 mg
J3303	Injection, triamcinolone hexacetonide, per 5 mg
J1095	Injection, dexamethasone acetate, per 8 mg

7.1 Medicare

The Centers for Medicare and Medicaid Services (CMS) provided the results of a query aimed to enumerate the frequency of ESI over the period January 2009- March 2014 for beneficiaries aged 65 or older. The beneficiary must have been continuously enrolled in Parts A and B for two days prior to the index date. The index date for epidural injection must have occurred within 2 days of receiving at least one injectable J-code, and vice versa.

Over the approximately 5 year study period, 6.6 million ESI were administered to 1.4 million patients over the age of 65 years. Figure 5 below depicts the number of ESI per month during the study period.

Figure 5. Number of Epidural Injections per Month in Medicare January 2009-March 2014



The non-transforaminal approach was slightly more commonly used than the transforaminal approach (52% of injections vs. 48% of injections, respectively). Over the five year period, the number of ESI trended upward modestly (no statistical testing was done to confirm this observation). The age distribution of recipients for ESI was 52% in age 65-74, 36% in age 75-84, and 12% in age 85+; the sex distribution was 63% female and 37% male. The interquartile range (25-75%) for number of ESI in a calendar year was 1-3. In a given year, 95% of patients had eight ESI or fewer.

7.2 Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the FDA to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products. Mini-Sentinel uses pre-existing administrative and claims data from multiple sources. Mini-Sentinel is part of the FDA's Sentinel Initiative, which is exploring a variety of approaches for improving the Agency's ability to quickly identify and assess safety issues.

FDA requested an estimate of the frequency of epidural steroid injections in the Mini-Sentinel Distributed Database (17 data partners encompassing 175 million patients) This database is not designed to be representative of the US population, and therefore the number of recipients identified is less important than their characteristics. FDA's desire was to use Mini-Sentinel data to characterize recipients of ESI in the younger population, but covered by commercial insurance.

Epidural steroid use was defined as at least one HCPCS code defining the procedure and at least one HCPCS code defining the product within two days of each other. The time window for the request was January 1, 2000 to June 30, 2013; however, because the number of patients in the Mini-Sentinel Distributed Database varies by year, only the total number and characteristics of ESI from the most recent full year of data are presented (2012).

In 2012, among patients 0-59 years old in the MS distributed database with a minimum of medical coverage and in any care setting (combined inpatient and outpatient), there were 262,301 ESI (using codes listed above) among 150,572 patients. Among these 150,572 recipients of ESI, 54% were female. ESI were administered more frequently with age; 44% of ESI were administered to patients 50-59 years old and 32% of ESI were administered to patients 40-49 years old. The transforaminal approach was utilized for 42% of the ESI in that year.

FDA will be exploring further possibilities for obtaining national estimates of use in the U.S. population under the age of 65 years, and will present these to the committee if available by the meeting date. It is clear, however, from the utilization data that ESI are widely administered, particularly in middle-aged to elderly patients, with many receiving more than one such injection.

8 FDA's Safe Use Initiative and the Recommendations from the Expert Working Group

To address concerns related to medication-related risks, the FDA created its Safe Use Initiative (SUI) in 2009 to create and facilitate public and private collaborations within the healthcare community. The goal of the SUI is to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing and evaluating cross-sector innovations with partners who are committed to safe medication use. It works with stakeholders to respond to the challenges of managing risks associated with the way medications are used.

SUI facilitated the organization of an expert Working Group of key stakeholders created to understand the causes of the neurologic injuries associated with epidural steroid injections and devise strategies to mitigate their risk. The Working Group consisted of experts external to the FDA who have published scientific studies or scholarly works on the topic of epidural steroid injections, and SUI representatives helped convene and facilitate meetings without actively participating in the deliberations or decision-making process.

Members of the Working Group include the following: James P. Rathmell, M.D. (Lead), Honorio T. Benzon, M.D. (Co-lead), Charles Aprill, M.D., Nikolai Bogduk, M.D., Paul Dreyfuss, M.D., Marc Huntoon, M.D., M.D., Daniel Riew, M.D., Richard Rosenquist, M.D., Natalia S. Rost, M.D., Ph.D., and Mark Wallace, M.D. The Working Group drafted, discussed, and formulated a set of clinical considerations to minimize the risk of catastrophic neurological injury associated with epidural steroid injections. Following the development of the initial set of clinical considerations, input was sought from national medical organizations whose members are involved in the care of patients with spinal pain syndromes. The purpose of these clinical considerations is to provide guidance to medical practitioners, not to inform a particular regulatory action.

The preliminary clinical considerations from this Working Group were presented orally in a panel session titled "Transforaminal Epidural Steroid Injections & the FDA Safe Use Initiative" that was held during the American Society of Anesthesiologists (ASA) 2013 Annual Meeting in San Francisco, CA on October 12, 2013.

Following the ASA meeting, the clinical considerations were further discussed by the Working Group and the representatives of the national medical organizations described above, and have been assembled into a manuscript and submitted for publication; the manuscript is in the peer review process.

8.1 Chronology of FDA Safe Use Initiative (SUI) interactions with the Epidural Steroid Injection (ESI) Expert Working Group[†] and the national medical organizations

April 2011	<ul style="list-style-type: none"> • Discussion held between SUI and Dr. Rathmell regarding the catastrophic neurologic adverse events of epidural steroid injections and best practices/guidelines in place • Decision made to gather a group of experts from different specialties to discuss the issue. • Dr. Rathmell recommended a list of experts
Nov 2011	<ul style="list-style-type: none"> • First teleconference held with expert group: SUI oriented the group to SUI's mission and objectives; initial discussion of ESI safety
March 2012	<ul style="list-style-type: none"> • Second teleconference: discussion of a plan to move forward to draft a list of practice measures upon which to seek consensus • Decision made to invite national pain management organizations for input on the practice measures document
Aug-Dec 2012	<ul style="list-style-type: none"> • Practice measures document sent to national pain management organizations for input • Responses received from national pain management organizations
Jan 2013	<ul style="list-style-type: none"> • Meeting with the expert group and representatives of pain management organizations to go through the responses received from the organizations.
June 2013	<ul style="list-style-type: none"> • Decision made to present developing practice measures document at the annual American Society of Anesthesiologists (ASA) meeting
Sept 2013	<ul style="list-style-type: none"> • Meeting with expert panel and pain management organizations' representatives for final input on the practice measures document
Oct 2013	<ul style="list-style-type: none"> • Presentation at ASA meeting on expert panel activities including discussion of the organizational voting on practice measures
Dec 2013	<ul style="list-style-type: none"> • First draft of manuscript with practice measures recommendations completed
Winter-Spring 2014	<ul style="list-style-type: none"> • Manuscript undergoes revision
May 2014	<ul style="list-style-type: none"> • SUI presents information about its mission and objectives to the Multi-Society Pain Workgroup*
Sept-Oct 2014	<ul style="list-style-type: none"> • Manuscript submitted to a peer-reviewed journal for publication

*The leadership of the expert panel sought the input of the Multi-Society Pain Workgroup (that had been convened for other purposes by CMS)

9 Regulatory Requirements and Guidance Recommendations for the Relevant Sections of the Product Labeling

A familiarity with the pertinent regulatory requirements and guidance recommendations of the prescribing information is important for determining how the risk information about serious neurologic adverse events should be communicated in the injectable corticosteroid labeling.

9.1 Prescribing Information

The prescribing information is written for healthcare providers and must:[58]

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug,
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular, and
- Be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

9.2 Adverse Reactions

For the purposes of prescription drug labeling, an adverse reaction (AR) is an undesirable effect reasonably associated with the use of the drug. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.[59]

9.3 Boxed Warning

The BOXED WARNING section of the labeling must be the first section in the FULL PRESCRIBING INFORMATION, must be surrounded by a “box” (i.e., a single black line), and must contain “contraindications or serious warnings, particularly those that may lead to death or serious injury.”[60] This section must briefly explain the clinically significant adverse reaction or risk and refer to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections. A boxed warning is ordinarily used to highlight for prescribers one of the following situations:[1]

- There is an AR so *serious*^[j] in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling AR) that it is essential that it be considered in assessing the risks and benefits of using a drug;
- There is a serious AR [59] that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or

- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted [e.g., certain Elements to Assure Safe Use (ETASU) under Risk Evaluation and Mitigation Strategies (REMS)].

A boxed warning can also be used in other situations [60]:

- To highlight a warning that is especially important to the prescriber.
- For a drug that poses risk-benefit considerations that are unique among drugs in a drug class (e.g., when the drug is the only one in its class to have a particular clinically significant AR or risk and is indicated as a second line therapy because of that clinically significant AR or risk).

Boxed warnings are more likely to be based on observed serious AR, but there are instances when a boxed warning based on an expected AR would be appropriate. For example, an Embryofetal Toxicity boxed warning would be appropriate for a drug based on evidence in humans or animals that drugs in its pharmacologic class pose a serious risk of developmental toxicity during pregnancy, even though no AR was seen with the drug [60].

9.4 Warnings and Precautions

The WARNINGS AND PRECAUTIONS section should describe serious or clinically significant AR that have occurred with the drug or risks that are expected to occur (e.g., based on the drug class; animal data raise substantial concern about the potential occurrence of the AR in humans). This section “must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.”[61] The following factors can be used in determining if AR are clinically significant [60]:

- The relative seriousness of the disease or condition being treated.
 - Non-serious AR caused by drugs intended to treat minor, self-limiting conditions may be considered clinically significant.
 - However, those same AR caused by drugs intended to treat serious or life-threatening conditions (e.g., malignancies) may be considered much less clinically significant and not appropriate for inclusion in this section.
- A high absolute risk or rate of AR occurrence
- An AR that may lead to a potentially serious outcome unless an action is taken (e.g., dosage reduction or discontinuation) to prevent a serious outcome
- An AR that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy.
- An AR that can significantly affect patient compliance particularly when non-compliance has potentially serious consequences.

Each WARNINGS AND PRECAUTIONS subsection should include a succinct description of a topic and should contain the following (if known) [60, 61]:

- A succinct description of the serious or clinically significant AR or risk
- Known risk factors for the AR
- Outcome
- Numerical estimate of the risk or AR rate
- Steps to take to prevent, mitigate, monitor, or manage the AR

9.5 Contraindications

The CONTRAINDICATIONS section must describe situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal AR) clearly outweighs any possible therapeutic benefit. These situations include the use of the drug in a subpopulation of patients that have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed [62].

Contraindications may be based on [60]:

- Observed AR
- Anticipated AR supported by data (e.g., pharmacology, chemistry, or drug class data; or animal data) and the likelihood and severity of the AR.

10 References

Website and Product Labeling References

- A. <http://www.fda.gov/drugs/drugsafety/safeuseinitiative/default.htm>
- B. <http://www.fda.gov/Drugs/DrugSafety/ucm394280.htm>
- C. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm210293.htm>
- D. <http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm082129.htm>
- E. The Warning statement in the approved Kenalog-10 and Kenalog-40 labeling reads as follows, “Neurologic: Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration (see ADVERSE REACTIONS: Gastrointestinal and Neurologic/Psychiatric).”
- F. FDA Orange Book < <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm> > (accessed on October 22, 2014)
- G. Multistate outbreak of fungal meningitis and other infections. <http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/default.htm> (accessed October 22, 2014)
- H. <https://www.asahq.org/For-Members/Advocacy/Washington-Alerts/ASA-Formally-Responding-to-FDA-Warning-on-Injection-of-Corticosteroids-into-Epidural-Space.aspx>
- I. See the [*Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling*](#) guidance.

- J. For the purposes of prescription drug labeling, a *serious AR* is an AR that results in the following outcomes: Death, life-threatening AR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Furthermore, AR may be considered serious if they jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed in this definition. See the [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance.

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62. See 21 CFR 201.57(c)(5).

FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain

Safety Announcement

[4-23-2014] The U.S. Food and Drug Administration (FDA) is warning that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The injections are given to treat neck and back pain, and radiating pain in the arms and legs. We are requiring the addition of a *Warning* to the drug labels of injectable corticosteroids to describe these risks. Patients should discuss the benefits and risks of epidural corticosteroid injections with their health care professionals, along with the benefits and risks associated with other possible treatments.

Injectable corticosteroids are commonly used to reduce swelling or inflammation. Injecting corticosteroids into the epidural space of the spine has been a widespread practice for many decades; however, the effectiveness and safety of the drugs for this use have not been established, and FDA has not approved corticosteroids for such use. We started investigating this safety issue when we became aware of medical professionals' concerns about epidural corticosteroid injections and the risk of serious neurologic adverse events.¹ This concern prompted us to review cases in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature (see Data Summary).²⁻¹⁶

To raise awareness of the risks of epidural corticosteroid injections in the medical community, [FDA's Safe Use Initiative](#) convened a panel of experts, including pain management experts to help define the techniques for such injections which would reduce preventable harm. The expert panel's recommendations will be released when they are finalized.

As part of FDA's ongoing effort to investigate this issue, we plan to convene an Advisory Committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed.

Injectable corticosteroids include methylprednisolone, hydrocortisone, triamcinolone, betamethasone, and dexamethasone. This safety issue is unrelated to the contamination of compounded corticosteroid injection products reported in 2012.

Facts about corticosteroids

- A class of drugs commonly used to reduce swelling or inflammation
- Injectable corticosteroids include methylprednisolone, hydrocortisone, triamcinolone, betamethasone, and dexamethasone

- Corticosteroids are not approved by FDA for injection into the epidural space of the spine.

Additional Information for Patients

- Rare but serious problems have occurred after injection of corticosteroids into the epidural space of the spine to treat neck and back pain, and radiating pain in the arms and legs. These serious problems include loss of vision, stroke, paralysis, and death.
- The effectiveness and safety of injection of corticosteroids into the epidural space of the spine have not been established, and FDA has not approved corticosteroids for this use.
- Discuss the benefits and risks of epidural corticosteroid injections with your health care professional, along with the benefits and risks associated with other possible treatments.
- Seek emergency medical attention immediately if you experience any unusual symptoms after receiving an epidural corticosteroid injection, such as loss of vision or vision changes; tingling in your arms or legs; sudden weakness or numbness of your face, arm, or leg on one or both sides of the body; dizziness; severe headache; or seizures.
- Report any side effects from epidural corticosteroid injections to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Rare but serious neurologic adverse events have been reported with epidural corticosteroid injections, including spinal cord infarction, paraplegia, quadriplegia, cortical blindness, stroke, and death.
- These serious neurologic events have been reported with and without the use of fluoroscopy.
- The effectiveness and safety of epidural administration of corticosteroids have not been established, and FDA has not approved corticosteroids for this use.
- Discuss with patients the benefits and risks of epidural corticosteroid injections and other possible treatments.
- Counsel patients to seek emergency medical attention immediately if they experience symptoms after receiving an epidural corticosteroid injection, such as loss of vision or vision changes; tingling in their arms or legs; sudden weakness or numbness in their face, arm, or leg on one or both sides of the body; dizziness; severe headache; or seizures.
- Report adverse effects following epidural corticosteroid injections to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA reviewed a sampling of cases from the FDA Adverse Event Reporting System (FAERS) database, as well as cases in the medical literature of serious neurologic adverse events associated with epidural corticosteroid injections.²⁻¹⁶ Serious adverse events included death, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, stroke, seizures, nerve injury, and brain edema. Many cases were temporally associated with the corticosteroid injections, with adverse events occurring within minutes to 48 hours after the corticosteroid injections. In some cases, diagnoses of neurologic adverse events

were confirmed through magnetic resonance imaging or computed tomography scan. Many patients did not recover from these reported adverse events.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Review

Date: October 28, 2014

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Product Name(s): Epidural Steroid Injections

Subject: Serious Neurological Events and Arachnoiditis

Application Type/Number: Multiple

Applicant/Sponsor: Multiple

OSE RCM #: 2014-1621

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EXECUTIVE SUMMARY

This review evaluates cases identified in the FDA Adverse Event Reporting System (FAERS) database and published medical literature for an association between serious neurologic adverse events and epidural steroid injections (ESIs). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that DPV provide an up-to-date assessment of the FAERS data and the medical literature which describes ESIs and serious neurologic events, and also provide an assessment of a potential association of arachnoiditis with injectable corticosteroids.

DPV's analysis of the FAERS cases (including 18 published case reports¹⁻¹⁸) and the medical literature suggests an association between the use of ESIs and serious neurologic adverse events. We identified 131 FAERS cases of serious neurologic adverse events, including 41 cases of arachnoiditis. Serious neurologic adverse events, in addition to arachnoiditis, included paraparesis/paraplegia, quadriplegia, spinal cord infarction, stroke, thrombosis/thromboembolism, sensory disturbances, nerve injury, blindness, seizures, bowel/bladder dysfunction and psychological/behavioral changes. FAERS data and the medical literature suggest that use of imaging does not eradicate the risk of serious neurologic outcomes, though it may reduce this risk.

Medical organizations and other groups outside of FDA often refer to injectable steroids as either "particulate" (methylprednisolone acetate, triamcinolone acetonide or hexacetonide, betamethasone acetate, betamethasone acetate/betamethasone sodium phosphate) or "non-particulate" (dexamethasone sodium phosphate, betamethasone sodium phosphate, methylprednisolone sodium succinate, hydrocortisone sodium succinate). For the purpose of this review, we considered the suspensions to be "particulates" and the solutions to be "non-particulates". While serious neurologic adverse events were reported with both types of preparations, the case series for this review contained many more reports for "particulate" steroids (n = 116) compared with "non-particulate" steroids (n = 4). Eleven cases did not report a formulation. It is not known whether this difference reflects greater utilization of "particulate" steroids or greater toxicity. All five of the cases reporting a fatal outcome in the case series reported the use of "particulate" steroids, although the cause of death in two cases (both reporting arachnoiditis) was due to completed suicide.

The published medical literature regarding the use of ESI is extensive, although much of it focuses on efficacy. It is acknowledged by virtually all authors that serious neurologic events can occur in association with ESI. Although there is no generally agreed upon estimate of frequency, these events are generally considered to be rare. Despite the fact that there are published cases of serious neurologic events in diverse settings, there is a general consensus that transforaminal injections are riskier than interlaminar or caudal injections, "particulate" steroids are more likely to lead to embolic events if injected intravascularly than "non-particulates," and imaging to confirm appropriate needle placement prior to injection is of value. However, there are no large clinical studies that demonstrate a single approach or formulation as being safer than another.

The 41 FAERS cases of arachnoiditis reported with ESI use did not provide sufficient clinical detail to make a reasonable assessment regarding causality. The majority of reports were submitted by consumers (n=37) and 39 cases reported “particulate” corticosteroid injection. Only one case reported a route (interlaminar) and seven cases reported the injection site (1 cervical, 4 lumbar, 1 lumbar/sacral, 1 sacral).

In summary, serious or catastrophic neurologic events following ESI are reported in a broad range of settings and no single mode of administration has been identified as free of risk with any reasonable degree of certainty. Most cases reported administration of a “particulate” steroid and there was an imbalance seen for transforaminal injections, compared with the interlaminar or caudal routes. However, any implication for differential risk is limited due to lack of reliable information about utilization of different formulations or routes of administration.

It is important to note that FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

1 INTRODUCTION

This review evaluates cases identified in the FDA Adverse Event Reporting System (FAERS) database and published medical literature for an association between serious neurologic adverse events and epidural steroid injections (ESIs). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that DPV provide an up-to-date assessment of the FAERS data and the medical literature which describe ESIs and serious neurologic events, and also provide an assessment of a potential association of arachnoiditis with injectable corticosteroids.

1.1 BACKGROUND

In November 2009, the Division of Analgesia, Anesthesia, and Rheumatology Products (DAARP) received correspondence from Dr. James Rathmell, an anesthesiologist at Harvard University, detailing concerns regarding a possible association of depot formulations of steroids for transforaminal epidural injections with catastrophic neurologic injuries when these depot steroids were inadvertently injected intra-arterially. DAAAP asked the Office of Surveillance and Epidemiology (OSE) to conduct an FDA Adverse Event Reporting System (FAERS) search (formerly known as AERS) for reports of injectable corticosteroid products (betamethasone, dexamethasone, hydrocortisone, methylprednisolone, and triamcinolone) and serious neurologic events (e.g., stroke, spinal cord infarction, quadriplegia) associated with epidural injections.

- May 14, 2010 - OSE completed a review of neurologic events with epidural injection of corticosteroids¹⁹
- February 14, 2011 - OSE completed a review of neurologic events with epidural injection of local anesthetics²⁰
- February 23, 2011 - OSE completed a review of medication errors with epidural injection²¹
- June 8, 2011 - Bristol-Myers Squibb (Kenalog-10, triamcinolone acetonide) submitted a Changes Being Effected (CBE) supplement. BMS proposed addition of the following language to the Kenalog label: ***Not for intravenous, intramuscular, intraocular, epidural or intrathecal use*** and, under Warnings (Neurologic): *Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events have been associated with epidural and intrathecal routes of administration.*
- July 2014 – Sponsors of ESIs provided revisions to labeling that reflect the risk of serious neurologic adverse reactions with ESIs:

WARNINGS: Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids (see WARNINGS: Neurologic). Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

DPV has provided previous reviews evaluating safety of ESIs, however this review is a broader and up-to-date assessment of serious neurologic events.

2 REGULATORY HISTORY

2.1 PRODUCT LABELING

No steroid preparation has a marketing indication for epidural use; however, literature indicates the procedure has been used since at least 1961. See Appendix A for steroid products approved for injection.

Betamethasone acetate and betamethasone sodium phosphate (Celestone Soluspan), Dexamethasone sodium phosphate (West-Ward, American Regent, Inc, Fresenius Kabi USA, Mylan), Hydrocortisone sodium succinate (Solu-Cortef), Triamcinolone acetonide (Kenalog), Methylprednisolone acetate (Depo-Medrol), and Methylprednisolone sodium succinate (Solu-Medrol):

WARNINGS: *Serious Neurologic Adverse Reactions with Epidural Administration:* Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

Triamcinolone acetonide (Kenalog):

WARNINGS: Neurologic:

Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration (see **ADVERSE REACTIONS: Gastrointestinal and Neurologic/Psychiatric**).

Adverse Reactions: Neurologic/Psychiatric:

Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychiatric disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration. Spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke (including brainstem) have been reported after epidural administration of corticosteroids (see **WARNINGS: Neurologic**).

Methylprednisolone acetate (Sandoz):

Adverse Reactions: Intrathecal/Epidural: Arachnoiditis

Corticosteroid Preparations²

Medical organizations and other groups outside of FDA have described parenteral steroid preparations as “particulate” and “non-particulate.” Most corticosteroid preparations contain corticosteroid esters, which are highly insoluble in water; forming microcrystalline suspensions (i.e., “particulate”). “Particulate” corticosteroid preparations include methylprednisolone acetate, triamcinolone acetonide or hexacetonide, betamethasone acetate, and betamethasone acetate/betamethasone sodium phosphate. Ester containing formulations have a larger particle size.

Dexamethasone sodium phosphate, betamethasone sodium phosphate, methylprednisolone sodium succinate, and hydrocortisone sodium succinate are non-ester corticosteroid formulations which are freely soluble in water (i.e., “non-particulate”).

2.1 PREVIOUS DIVISION OF PHARMACOVIGILANCE REVIEW REGARDING SERIOUS NEUROLOGICAL EVENTS REPORTED WITH EPIDURAL STEROID INJECTIONS

“Catastrophic Neurologic Outcome after Transforaminal Epidural Steroid Injection” (Lee J, Hausman E)¹⁹

DPV completed a safety review on May 14, 2010, which evaluated postmarketing cases of catastrophic neurologic adverse events reported with transforaminal epidural steroid injections. The Adverse Event Reporting System (AERS) database was searched on December 23, 2009, from approval dates for domestic reports of epidural steroid injection products using selected MedDRA preferred terms (see Appendix B). A sample of 248 reports from 1022 initial AERS reports were evaluated and 21 of these cases met the inclusion criteria: methylprednisolone (8), triamcinolone (7), betamethasone (4), and dexamethasone (2). There were no cases of catastrophic neurologic adverse events associated with hydrocortisone injections. There were five deaths associated with the use of “particulate” steroids while no deaths were reported with “non-particulates”, and intravascular involvement was specifically mentioned in all five cases. The neurologic complications reported in these death cases were brain stem infarction (3), grand mal convulsion (1), and brain edema/seizure (1). A search of case reports in the medical literature was performed on December 17, 2009, and January 27, 2010. Eleven references reported 13 unique incidents of catastrophic neurologic adverse events occurring during or within 48 hours of the procedure; a 14th case was excluded for failure to identify the injected steroid. One or more catastrophic events were found for betamethasone, hydrocortisone, methylprednisolone, and triamcinolone. No catastrophic events were found for dexamethasone.

Based on the findings in AERS and literature data, DPV determined there was an association between catastrophic neurologic events and transforaminal epidural injections of both “particulate” and “non-particulate” corticosteroid products. DPV recommended a drug safety communication to warn of potential neurologic complications following administration of transforaminal epidural “particulate” and “non-particulate” corticosteroid injections.

3 METHODS AND MATERIALS

3.1 CASE DEFINITIONS

Serious Neurologic Event

For the purposes of this update, we included cases that reported a temporal relationship with an ESI and one of the following criteria:

- Serious neurologic adverse event
- Worsening of pre-existing pain

We excluded cases that reported either of the following:

- Alternative etiologies (e.g., fungal meningitis from contaminated steroid injections)
- Spinal surgery shortly before the diagnosis of neurological adverse event

Arachnoiditis

Reports were included in the arachnoiditis case series if the report described “arachnoiditis” following ESI without a preceding diagnosis of arachnoiditis.

We excluded cases that reported either of the following:

- Alternative etiologies (e.g., fungal meningitis from contaminated steroid injections)
- Spinal surgery shortly before the diagnosis of arachnoiditis

3.2 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1 for reports of serious neurological disorders with ESI use.

Table 1. FAERS Search Strategy*	
Date of search	April 23, 2014
Time period of search	November 1, 1997 [†] through April 23, 2014
Product Terms	Active ingredient: betamethasone, betamethasone acetate, betamethasone sodium phosphate, dexamethasone, dexamethasone acetate, dexamethasone phosphate, dexamethasone sodium phosphate, hydrocortisone, hydrocortisone acetate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, methylprednisolone sodium phosphate, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide
Search criteria	serious, domestic
Narrative term search	epidural, transforaminal, translaminar, interlaminar, caudal

* See Appendix C for description of the FAERS database.

[†] FAERS searches do not display case narratives of reports submitted to FDA prior to November 1, 1997, therefore only reports submitted to FDA after this date were included so that narrative terms of interest can be searched.

FAERS was also searched with the strategy described in Table 2 for reports of arachnoiditis with ESI use.

Table 2. FAERS Search Strategy*	
Date of search	April 23, 2014
Time period of search	Up to April 23, 2014
Product Terms	Active ingredient: betamethasone, betamethasone acetate, betamethasone sodium phosphate, dexamethasone, dexamethasone acetate, dexamethasone phosphate, dexamethasone sodium phosphate, hydrocortisone, hydrocortisone acetate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, methylprednisolone sodium phosphate, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide
Preferred Term (PT)	arachnoiditis
Search criteria	serious, domestic

3.3 LITERATURE SEARCH

The medical literature was searched with the strategy described in Table 3 and 4. In addition to identifying additional cases, the purpose of the literature review was to identify recent, focused studies, articles, or commentaries providing information about the risks associated with epidural steroid injections. The larger goal was to ascertain whether there was a “consensus” opinion on risks. A second, more specific search was done to focus on a possible association between epidural steroid injections and arachnoiditis.

Table 3. Literature Search Strategy	
Date of search	August 1, 2014
Database	PubMed
Search Terms	epidural, steroid, adverse, safety, transforaminal, interlaminar, caudal
Years included in search	August 1, 2012 – August 1, 2014

* In light of the large number of publications retrieved, we limited the search to include only publications over the past two years

Table 4. Literature Search Strategy	
Date of search	Oct 20, 2014
Database	PubMed
Search Terms	Epidural steroid injection, arachnoiditis
Years included in search	All

4 RESULTS

4.1 FAERS CASE SELECTION

The FAERS search retrieved 476 reports; 389 reports related to serious neurological adverse events and 87 reports related to arachnoiditis. Four reviewers (Laurelle Cascio, PharmD, Sara Camilli, PharmD, Jane Gilbert, MD, PhD, and Allen Brinker, MD) were assigned to review reports as potential cases. The initial screen included an assessment for a serious neurologic event in close temporal association to ESI procedure OR a diagnosis of arachnoiditis following ESI. After applying the case definition in Section 2 and accounting for duplicate reports, 90 cases were included in the case series of a serious neurologic adverse event and 41 cases were included in the case series of arachnoiditis with ESI use for a total of 131 cases (see Figure 1).

Figure 1. FAERS Case Selection

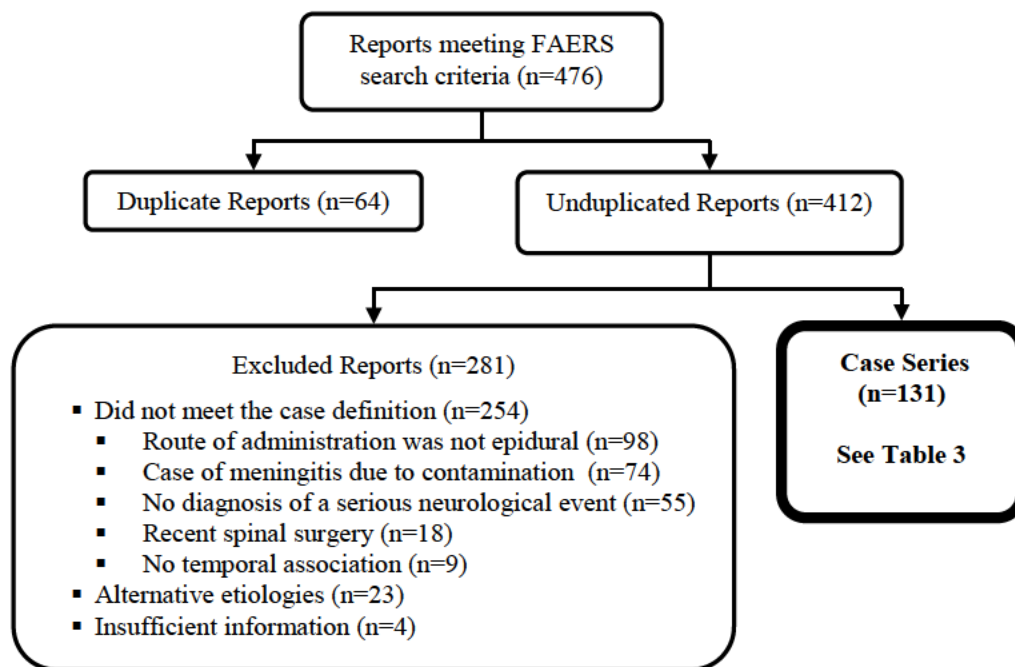


Table 5 summarizes the 90 FAERS cases of serious neurologic adverse events reported with ESI use for this case series.

Table 5. Descriptive characteristics of FAERS cases of serious neurologic adverse events, excluding arachnoiditis, reported with ESI use, received by FDA from November 1, 1997 – April 23, 2014 (N=90)		
Age (years) (n=79)	Mean	56.4
	Median	54
	Range	23-89
Gender (n=75)	Female	49
	Male	26
FDA Receipt Date	1997-2002	16
	2003-2008	32
	2009-2014	42
Report type	Expedited	59
	Direct	25
	Periodic	6
Reporter	Health Care Provider	43
	Consumer	47
Reported Primary Outcome	Death	3
	Hospitalization	35
	Life Threatening	1
	Disability	17
	Other serious	34
Steroid reported (n=88)	Methylprednisolone	45
	Triamcinolone	37
	Betamethasone	3
	Dexamethasone	3
Epidural route (n=22)	Transforaminal	15
	Interlaminar	5
	Caudal	2
Time to onset from start of therapy (n=62)	Within 1 day	47
	1 day – 1 month	13
	1 month – 6 months	1
	6 months – 1 year	1
Anesthetic administered* (n=35)	Bupivacaine	21
	Lidocaine	19
	Ropivacaine	1
Anesthetic route of administration (n=22)	Epidural	20
	Local	1
	Epidermal and local	1
Imaging (n=33)*	Contrast Agent	23
	Fluoroscopy	21
	Computed tomography	2
	Angiography	2

Table 5. Descriptive characteristics of FAERS cases of serious neurologic adverse events, excluding arachnoiditis, reported with ESI use, received by FDA from November 1, 1997 – April 23, 2014

(N=90)		
Injection Site (n=54)	Cervical	22
	Cervical/Thoracic	3
	Cervical/Lumbar	3
	Thoracic	1
	Thoracic/Lumbar	2
	Lumbar	19
	Lumbar/Sacral	3
	Sacral	1
Event Outcome (n=43)	Persisted	34
	Resolving/Resolved	9

*Not mutually exclusive

Table 6 summarizes the 41 FAERS cases of arachnoiditis reported with ESI use for this case series.

Table 6. Descriptive characteristics of FAERS cases of arachnoiditis reported with ESI use, received by FDA, up to April 23, 2014

(N=41)		
Age (years) (n=26)	Mean	45
	Median	46
	Range	32-57
Gender (n=35)	Female	19
	Male	16
FDA Receipt Date	1985-1994	2
	1995-2004	17
	2005-2014	22
Report type	Expedited	11
	Direct	20
	Periodic	10
Reporter	Health Care Provider	4
	Consumer	37
Reported Primary Outcome	Death	2
	Hospitalization	11
	Disability	17
	Required Intervention	1
	Other serious	10
Steroid reported	Methylprednisolone	35
	Triamcinolone	4
	Betamethasone	2
Epidural route (n=1)	Interlaminar	1

Table 6. Descriptive characteristics of FAERS cases of arachnoiditis reported with ESI use, received by FDA, up to April 23, 2014 (N=41)		
Time to onset from start of therapy (n=11)	Within 1 day	3
	1 day – 1 month	5
	1 month – 1 year	3
Anesthetic administered* (n=5)	Bupivacaine	5
	Lidocaine	1
Anesthetic route of administration (n=2)	Epidural	2
Imaging (n=3)	“No imaging/fluoroscopy”	2
	Contrast Media	1
Injection Site (n=7)	Cervical	1
	Lumbar	4
	Lumbar/Sacral	1
	Sacral	1
Event Outcome (n=17)	Persisted	17

*Not mutually exclusive

Appendix D lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 131 cases in this case series.

The 41 cases of arachnoiditis reported with ESI use did not provide sufficient clinical detail to make a reasonable assessment regarding causality. The majority of reports were submitted by consumers (n=37) and 39 cases reported “particulate” corticosteroid injection. Only one case reported a route (interlaminar) and seven cases reported the injection site (1 cervical, 4 lumbar, 1 lumbar/sacral, 1 sacral).

See Appendix E for a summary of the case series.

Selected Cases

Cases illustrating serious neurologic events that occurred despite fluoroscopic guidance; neither case involved an injected anesthetic.

FAERS Case # 6215391 – A 41-year-old male with a history of neck pain, remote intravenous drug abuse, hepatitis C, and cervical spondylitis experienced a fatal brainstem stroke following a cervical epidural injection of methylprednisolone acetate. The injection was performed by an experienced anesthesiologist under fluoroscopic guidance and without sedation. A test injection was performed with nonionic contrast prior to steroid injection, confirming proper needle placement in the posterior epidural space. The patient received methylprednisolone 40 mg with preservative-free saline. The patient developed nausea, vomiting, and headache within minutes of the procedure. He deteriorated clinically and became unresponsive, and subsequently died seven days after methylprednisolone administration. Autopsy confirmed a brain stem infarction.

FAERS Case # 6006777 - A 53-year-old man with a history of chronic cervical pain and multilevel degenerative disc disease with multiple posterior disc protrusions received a cervical transforaminal injection of triamcinolone for pain relief. Fluoroscopy of the left C6 nerve root

sheath of injectable contrast was confirmed. Approximately 10 to 15 minutes following the procedure, he noted weakness in his left arm and bilateral lower limbs. MRI revealed a diffuse vascular infarct to the cervical cord, resulting in motor-incomplete tetraplegia.

Cases illustrating reports of serious neurologic events that occurred after receiving a lumbar ESI:

FAERS Case # 7257963¹³ - An 83-year-old female experienced paraplegia following image-guided transforaminal lumbar spine ESI. Relevant concomitant medications included NSAIDs, gabapentin, and hydrocodone for multilevel degenerative disc disease. The patient had no medical history of lower extremity numbness or weakness. The patient was given bupivacaine and Celestone Soluspan (betamethasone sodium phosphate/acetate) 6 mg with fluoroscopy. No arterial or venous uptake and no subarachnoid spread were observed. Immediately after the needle was withdrawn after infusion of the drug, the patient experienced lower extremity numbness and weakness. Two days later, an MRI revealed an acute spinal cord infarction. Eighteen months after the incident, the patient continued to have a neurogenic bladder and neurogenic bowel as well as impaired sensation in both lower extremities. She had partial motor recovery and progressed to ASIA grade D spinal cord injury.

FAERS Case # 8939941¹⁷ - A 63-year-old male experienced a spinal cord infarction following right sided lumbar transforaminal ESI for low back pain. Relevant medical history included prior ESIs without complications for low back pain with radicular symptoms. The patient was given betamethasone (formulation unknown) 12 mg in Lidocaine 1% once through L3-L4 fluoroscopic guidance. No concomitant medications were reported. On an unknown date the patient experienced spinal cord infarction leading to loss of sensory and motor function in lower extremities. MRI revealed a spinal cord infarct. On an unknown date, the patient was discharged with power wheel chair mobility and he required assistance for daily activities.

Cases illustrating reports of serious neurologic events that occurred after receiving an interlaminar ESI:

FAERS Case # 8919983¹⁸ - A 66-year-old female developed a spinal epidural hematoma and tetraplegia after receiving a cervical interlaminar ESI with methylprednisolone (formulation unknown) for upper extremity radicular pain. Relevant medical history included chronic renal insufficiency, multi-level neuroforaminal stenosis and degenerative discs. Concomitant medications included ketorolac 30 mg intramuscularly. Immediately after receiving methylprednisolone 80 mg with saline 4 ml, the patient reported significant spasm pain with no neurologic status changes. She underwent bilateral C5-T6 laminectomy with epidural hematoma evacuation and was discharged to acute inpatient rehabilitation. The event outcome was not reported.

FAERS Case # 7576635¹⁵ - A 52-year-old female experienced syrinx formation with focal myelomalacia after receiving a CEI with triamcinolone acetonide for chronic neck pain. She had received multiple epidural injections in the past and was hospitalized for management of complications arising from an interlaminar CEI. The procedure had been performed with

intravenous sedation (midazolam and propofol) under fluoroscopic guidance. A twenty gauge epidural needle was inserted at the C7-T1 level. Contrast flow showed “appropriate epidural spread” after triamcinolone 80 mg and preservative-free saline was injected. On awakening from sedation, the patient was unable to move her right side and complained of right hemisensory loss below the neck. Radiologic contrast showed “excellent epidural spread from T3 up in through C6.” The patient was treated with high-dose steroids followed by maintenance therapy. Over the next few hours her symptoms improved, although she required catheterization for urinary retention.

FAERS Case # 9122698 – A 58-year-old male experienced seizures, transient blindness, head pain, vertigo, muscle weakness, and mood changes one month after receiving an interlaminar CEI with betamethasone sodium phosphate (dose unknown) with fluoroscopy. An event outcome was not reported and no further information was reported.

Cases illustrating reports of serious neurological events that occurred after receiving a caudal ESI:

FAERS Case # 9797130 – A 39-year-old male experienced peripheral neuropathy, urinary retention, arthralgia, and genital and lower extremity hypoaesthesia within 24 hours after receiving a caudal ESI of methylprednisolone acetate (dose unknown) for back pain. Infection was ruled out and the events continued at the time of reporting. No further information was provided.

FAERS Case # 7243120 – A 35-year-old female experienced avascular necrosis of the hips, bowel and bladder dysfunction, peripheral sight problems, and memory impairment one month after receiving a caudal injection of methylprednisolone acetate for lower back pain from a fall. Marcaine 25% was also injected (route unknown). The patient had received a total of four caudal ESI within the same year. The outcome of the events continued at the time of reporting. No further information was provided.

Case illustrating report of arachnoiditis that occurred after receiving an ESI:

FAERS Case # 9034344 - A 44-year-old male experienced chronic pain, arachnoiditis, paresthesias, “cauda equina [*sic*]”, stenosis and fibrosis after receiving a CESI with triamcinolone (Kenalog-80) without fluoroscopy for shoulder pain. The event outcome was not reported and no further information was provided.

4.1.1 Additional Findings

Although cases that did not report a serious neurological event were excluded from our case series, two cases of spinal epidural lipomatosis (SEL) were reported. However, because SEL can be caused by overexposure to corticosteroids (administered by various routes), we provide a summary of these cases here.

The first case is a 56-year-old male who developed SEL after receiving a single, caudal epidural injection of triamcinolone for back and lower limb pain. Pertinent medical history included

Crohn's disease and depression, with no previous use of systemic steroids. His medications at presentation were amitriptyline and zaleplon. The patient's symptoms initially improved with the ESI, however, low back pain and left lower limb symptoms reoccurred 6-8 weeks after the injection and he developed new numbness and tingling in his limbs. Three months after the injection, a lumbar MRI demonstrated a new focal area of increased posterior epidural adipose tissue, which was causing thecal sac compression at the L5-S1 level. The patient continued to have intermittent episodes of bilateral lower extremity radiating pain.

The second case is a 68-year-old male who developed SEL after local epidural injections of methylprednisolone acetate and triamcinolone to treat lumbar stenosis. The patient experienced worsening pain following the third injection of triamcinolone 60 mg in the lumbar region. Three months later, an MRI revealed a substantial interval increase in epidural lipomatosis from L2 to L5 with significant compression of the thecal sac. The patient underwent laminectomies and a large amount of epidural fat was removed. Five months later, the patient's back and leg pain resolved.

4.2 LITERATURE SEARCH¹

In recent years, there has been a growing concern about the association between epidural steroid injections and the development of serious neurological adverse events such as spinal cord infarct, which may result in paraplegia, quadriplegia or even death. In order to identify published articles in the medical literature that would be informative about the association between epidural steroid injections (ESIs) and catastrophic adverse events, we conducted a search of the PubMed Database (see Table 3 and 4). A total of 192 published articles were retrieved.

The goal of this literature review was to identify articles to help discern if a "consensus view" about the safety of epidural steroid injections exists. Accordingly we did not limit our search only to case reports; nor did we limit it to reports of trials and studies. While we did include first hand case reports and *de novo* studies, we also included systematic literature reviews which we expected would capture useful information from earlier years. We excluded articles that dealt with infections that may have developed after an ESI, those reporting presence of a spinal cord tumor or other obvious confounders, and those that were deemed to be inapplicable to the subject of interest. Additional articles were identified in the course of the review that were not identified via the PubMed search, but which were clearly relevant, and were thus included in our evaluation.

As others have noted "legions of articles have been written on this subject" [19] and the purpose of the review was not intended to be exhaustive but reasonable in depth and breadth. An annotated bibliography including articles identified in the original PubMed search as well as additional articles identified in the course of the review is included in Appendix F. These are grouped into articles that focus on the cervical spine, the lumbar spine, or both. A single animal study and a single study concerning arachnoiditis follow. The remaining articles provide additional information about ESIs but do not necessarily address catastrophic safety issues.

¹ All references (including numbers in brackets) refer to the annotated bibliography in Appendix F.

Some of these additional articles summarize less catastrophic adverse events such as increases in salivary cortisol, vaginal bleeding or vertebral fracture.

4.2.1 Route of Injection

As compared with interlaminar (IL) and caudal injection, there appears to be a general consensus in the literature that regardless of location (cervical or lumbar) transforaminal (TF) injections are more risky and are more likely to lead to serious adverse neurologic events. However, serious neurologic events have been noted with the IL and caudal approach as well.

Ghai [7] contends that “catastrophic complications reported with the TF approach have raised concerns regarding its use.” Yet, it is commonly thought that TF injections are more effective than IL injections (DePalma [11]). To explore this issue, Ghai compared the parasagittal IL (PIL) route with the TF route (for lumbar ESIs) in 62 patients who were randomized to one of two arms. He reported that efficacy was about the same; there were no complications in either group, however 3 patients (or about 10%) in the TF group did have evidence of intravascular spread of contrast suggesting intravascular penetration which is thought to be potentially associated with serious neurologic events. Ilkhcoui and Koshkin [9] estimate the rate of intravascular penetration associated with the TF to be between 9 and 26%. Other publications evaluated for this review also show rates in this range.

Alternative approaches are not, however, free from vascular penetration and serious neurologic events. For example, Park [13] reported the results of a trial designed to compare ultrasound-guided vs fluoroscopy-guided caudal ESIs. A total of 55 subjects were randomized to two arms, ultrasound or fluoroscopy. The ultrasound arm had no evidence of intravascular penetration; however, there were 2 intravascular injections (3.6%) in the fluoroscopy arm, thus demonstrating that the caudal approach may also be associated with risk. The potential risk of the caudal approach is further underscored by Paik [15] who describes a case of cauda equina syndrome developing after caudal injection. With regard to the IL approach, Chen [14a] points out that there have been at least 3 cases of lumbar paraplegia after IL lumbar steroid injections wherein the proposed mechanism is hypothesized to be from the epidural needle penetrating the radiculomedullary artery. Cohen-Adad [4] states that a literature search conducted in 2011 revealed a “dozen published cases of cervical [spinal cord injury] after interlaminar approach to cervical ESI.” Finally, Ghai [14b] provides estimates of relative risk: “intravascular injection with lumbosacral transforaminal epidural steroid injection is reported to be 11.2% as compared with 1.2% after interlaminar epidural injection.”

4.2.2 Type of Steroid Preparation

Authors, medical organizations and other groups outside of FDA commonly characterize parenteral steroids as “particulate” and “non-particulate”. “Particulate” preparations include: triamcinolone acetonide or hexacetonide, methylprednisolone acetate, betamethasone acetate, and betamethasone acetate/betamethasone sodium phosphate. “Non-particulate” preparations include dexamethasone sodium phosphate, betamethasone sodium phosphate, methylprednisolone sodium succinate, and hydrocortisone sodium succinate.

There is a general consensus that “particulate” steroid preparations appear to present a higher risk for neurologic complications than do “non-particulate” steroid preparations when used as an ESI. The hypothesis is based upon the presumption that inadvertent vascular penetration with a “particulate” product (with particles larger than red blood cells) can lead to thromboembolism and subsequent spinal or brainstem infarct (Candido [3]). However, scientifically based evidence of comparative risk is lacking, in part, because most of the studies thus far conducted have used “particulate” preparations. Representative of the articles reviewed, Candido [3] concludes that “non-particulates” may be safer; he also points out that, of the “non-particulates”, dexamethasone is the only one *not* yet implicated in spinal cord or brainstem infarct following cervical ESIs.

There is one small animal study (Okubadejo [22]) that provides evidence to support the hypothesis that “particulate” steroid preparations are more likely to be associated with an adverse event than are “non-particulate” steroids. In this study, using fluoroscopy, 11 pigs underwent intentional injection of the vertebral artery; 4 of the pigs received a “particulate” steroid (methylprednisolone acetate) while 7 received “non-particulate” preparations (prednisolone sodium succinate or dexamethasone sodium phosphate). The four pigs who received a “particulate” steroid died, while the seven who received “non-particulate” formulations recovered.

4.2.3 Vertebral Artery/ Position of Needle

There is moderate agreement in the literature that for TF ESIs the position of the epidural needle in the foramen may increase or decrease the chances of a catastrophic adverse event. Stout [De Palma, 11] writes: “The risk of inadvertent intra-arterial injection varies by region of the spine...in the cervical spine, the vertebral artery lies within the intervertebral foramen at every spinal level and is in close proximity to the target for TF ESI. The vertebral artery is generally not encountered if the needle is kept in the posterior foramen...There, however, is anatomic variability...” And, as Tiso [6] points out, movement of the needle can occur.

Fitzgerald [2] summarizes a study attempting to assess the position of the vertebral artery relative to the trajectory of a typical cervical TF injection. He reports that the vertebral artery is commonly displaced into the foramen when there is advanced cervical degenerative disease. In his study of 68 patients (70 injections), the “needle trajectory intersected with the vertebral artery in 30 of 70 injections (46%) by CT-fluoroscopy.” Discussion of needle position suggests that imaging of the course of the vertebral artery could mitigate the risk of an adverse event. However, in his review of the literature, Popescu [5] points out that “posterior placement of the needle” did not preclude a bad outcome.

4.2.4 Blunt Needle

Though there is not extensive discussion of this point in the literature, use of a blunt needle has been suggested as one way to mitigate the risk of an ESI. The hypothesis is that if the needle is blunt, one would reduce the likelihood of vascular penetration and subsequent embolization.

Of note, Ilkhchoui and Koshkin [9] report the occurrence of intravascular injection despite the use of a blunt needle to administer a TF ESI at L5-S1. Candido [3] also cites evidence that blunt needles may “not be protective.”

4.2.5 Imaging

If inadvertent arterial or spinal cord injection is a mechanism leading to serious neurologic events, it follows that superior imaging could mitigate the risks of an ESI. The consensus of the literature is that better imaging would minimize risk. Fluoroscopy with and without CT, ultrasound (US) and digital subtraction angiography (DSA) have all been reviewed. To compare fluoroscopy with DSA, Hong [8] assessed 249 TF injections, 12.4 % of which were associated with intravascular penetration. Nine of the intravascular penetrations were not detected by fluoroscopy but were detected by DSA suggesting that DSA is a superior modality. However, the overall reliability of DSA in identification of the intravascular course is not known. Specifically, one can note that Chang Chien [16] reports a case of paraplegia after lumbar TF ESI despite DSA and fluoroscopy.

In another study, Hong [17] used fluoroscopy to confirm 251 ESIs; subsequently, he injected contrast. There were intradiscal injections in 6 patients (2.3%) and intravascular injections in 39 patients (15.5%). Detection of intravascular penetration with aspiration or static fluoroscopy with contrast was 20.5% and 51.2%, respectively, suggesting that neither method was overly reliable. As previously mentioned, Park [13] randomized 55 subjects to fluoroscopy or ultrasound. Intravascular injection occurred in 3.6% of fluoroscopy subjects while none occurred with ultrasound.

4.2.6 Arachnoiditis and ESIs

The literature search described in Table 4 identified a single case report (Nanjayan [23]) describing a case of arachnoiditis following caudal epidural steroid injections for lumbar radiculopathy. A few days after the injection, the patient presented with “contralateral sciatica, worsening low back pain and urinary retention ... followed by worsening motor functions in L4/L5/S1 myotomes ... [and] foot drop.” An MRI “suggested infective arachnoiditis.”

4.2.7 Literature: Conclusion

There is an extensive medical literature addressing the use of epidural steroid injections to relieve neck and back pain. The literature describes different locations (mainly cervical and lumbar), different routes of epidural administration (transforaminal, interlaminar, and caudal), different types of steroid preparations (“particulate” vs. “non-particulate”), different types of needles, and different positions of the needle vis-à-vis the vertebral or other arteries. For each of these factors, there is a consensus suggesting greater or lesser risk (e.g., cervical is riskier than lumbar, transforaminal is riskier than interlaminar, “particulate” steroids are riskier than “non-particulates”).

It is important to note, though, that strong scientific evidence to support these views is lacking. The comparative studies that have been conducted have been mainly focused on efficacy, not risk. In addition, the studies that have been conducted are too small to draw valid conclusions about the risk associated with different approaches. Kennedy (DePalma [11]) contends that “it

would take an estimated 796 patients to truly determine if no differences in efficacy existed between these [steroid] preparations.” Studies to determine the risk of a rare catastrophic adverse event such as paraplegia, quadriplegia, hemiparesis, or death would clearly require an even larger number of subjects.

Concerning arachnoiditis, a single case report has been retrieved from the literature. This is striking in comparison to the large number of reports and the extensive discussion of other neurologic events. Where arachnoiditis is elsewhere mentioned in the literature, it is usually characterized as resulting from intrathecal injection, not epidural injection.

5 DISCUSSION

DPV’s analysis of the FAERS cases (including 18 published case reports¹⁻¹⁸), and the medical literature suggests an association between the use of ESIs and serious neurologic adverse events. We identified 131 FAERS cases of serious neurologic adverse events, including 41 cases of arachnoiditis. Serious neurologic adverse events in addition to arachnoiditis included paraparesis/paraplegia, quadriplegia, spinal cord infarction, stroke, thrombosis/thromboembolism, sensory disturbances, nerve injury, blindness, seizures, bowel/bladder dysfunction and psychological/behavioral changes. FAERS data and discussions in the medical literature suggest that use of imaging does not eradicate the risk of serious neurologic outcomes, though it may reduce this risk.

Injectable steroids are commonly characterized as either “particulate” (methylprednisolone acetate, triamcinolone acetonide or hexacetonide, betamethasone acetate, betamethasone acetate/betamethasone sodium phosphate) or “non-particulate” (dexamethasone sodium phosphate, betamethasone sodium phosphate, methylprednisolone sodium succinate, hydrocortisone sodium succinate). For the purpose of this review, we considered the suspensions to be “particulates” and the solutions to be “non-particulates”. Serious neurologic adverse events, including arachnoiditis were reported with both types of preparations. However, “particulate” steroids were more often reported in association with serious neurological adverse events (n = 116) compared with “non-particulate” steroids (n = 4). Eleven cases did not report a formulation. It is not known whether this difference reflects greater utilization of “particulate” steroids or greater toxicity. All five fatalities reported the use of “particulate” steroids, although the cause of death in two cases (both reporting arachnoiditis) was due to completed suicide.

The published medical literature regarding the use of ESI is extensive, although much of it focuses on efficacy. It is acknowledged by virtually all authors that serious neurologic events occur. Though no specific estimate of the frequency of these events is commonly given they are generally described as rare in the literature. Most contend that risk is increased with transforaminal injections undertaken with “particulate” steroids and administered without imaging. However, strong scientific evidence for this is lacking. The controversy is well summarized by the debate between DePalma and Stout (DePalma[11]). In discussing the treatment of a specific patient, DePalma argues for the use of a lumbar transforaminal injection with “particulate” steroids while Stout recommends the same injection with (at least at the outset) a “non-particulate” steroid. DePalma’s argument is based on his contention that “particulate” steroids are more efficacious; he also believes that certain injection techniques

would prevent intravascular penetration. Stout cites studies showing the efficacy of “particulate” and “non-particulate” steroids to be approximately the same, and, because of the risk of intravascular injection, she recommends using “non-particulate” steroids, possibly followed by “particulate” steroids if there is a poor response.

Given the variety of ways in which ESIs can be administered (e.g., different approaches, different steroid preparations, different locations, different types of imaging, different volumes of injectate, etc.) there are many different combinations of variables that can describe a specific injection. It is not possible, at this time, to reasonably estimate the risk associated with each of these combinations of variables, and, one cannot say with reasonable certainty that one combination is better than another.

The 41 FAERS cases of arachnoiditis reported with ESI use did not provide sufficient clinical detail to make a reasonable assessment regarding causality. The majority of reports were submitted by consumers (n=37) and 39 cases reported particulate corticosteroid injection. Only one case reported a route (interlaminar) and seven cases reported the injection site (1 cervical, 4 lumbar, 1 lumbar/sacral, 1 sacral).

6 CONCLUSION

Serious or catastrophic neurologic events following ESI are reported in a broad range of settings and no single mode of administration has been identified as free of risk with any reasonable degree of certainty. Most cases reported administration of a “particulate” steroid and there was an imbalance seen for transforaminal injections, compared with the interlaminar or caudal routes. However, any implication for differential risk is limited due to lack of reliable information about utilization of different formulations or routes of administration.

It is important to note that FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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8 APPENDICES

8.1 APPENDIX A. APPROVED CORTICOSTEROID INJECTABLE PRODUCTS (REFERENCE LISTED DRUGS)

Drug	(A)NDA	Applicant (s)	FDA Approval	Solution or Suspension	Approved Route of Administration*				
					IA	IB	IL	IM	IV
Celestone Soluspan (betamethasone acetate; betamethasone sodium phosphate)	014602	Merck Sharp Dohme	3/3/1965	Suspension	X	X	X		
Dexamethasone (sodium phosphate)	084916 087440 087702 040491 040572 040802 040803	Fresenius Kabi USA Luitpold, Hikma Maple Fresenius Kabi USA Fresenius Kabi USA Agila SpecLts Agila SpecLts	9/6/1977 7/21/1982 7/7/1982 4/11/2003 4/22/2005 8/29/2008 8/29/2008	Solution	X		X	X	X
Kenalog-40 Kenaolg-10 (triamcinolone acetone)	014901 012041	Apothecon Apothecon	2/1/1965 1/4/1960	Suspension	X			X	
Aristospan (triamcinolone hexacetone)	16466	Sandoz	7/29/1969	Suspension	X		X		
Depo-Medrol (methylprednisolone acetate)	011757	Pharmacia & Upjohn	5/27/1959	Suspension	X		X	X	
Solu-Medrol (methylprednisolone sodium succinate)	011856	Pharmacia & Upjohn	5/18/1959	Powder for Solution	X		X	X	
Solu-Cortef (hydrocortisone sodium succinate)	009866	Pharmacia & Upjohn	4/27/1955	Powder for Solution				X	X

*IA (intra-articular), IB (intrabursal), IL (intralesional), IM (intramuscular), IV (intravenous)

8.2 APPENDIX B. MEDDRA SEARCH TERMS USED IN 2010 DPV REVIEW

Table 6. Selected PT list used for AERS search of steroid injections (N=107)

Anaesthetic Complication	Incorrect Route Of Drug Administration
Neurological	
Arachnoiditis	Infarction
Areflexia	Ischaemic Cerebral Infarction
Arterial Haemorrhage	Ischaemic Stroke
Arterial Injury	Motor Dysfunction
Blindness	Nerve Injury
Blindness Cortical	Nerve Root Injury
Brain Death	Neurogenic Bladder
Brain Hypoxia	Neurogenic Shock
Brain Injury	Neurological Decompensation
Brain Oedema	Neurological Examination Abnormal
Brain Stem Infarction	Neurotoxicity
Brain Stem Ischaemia	Paraesthesia
Cerebellar Infarction	Paralysis
Cerebellar Ischaemia	Paralysis Flaccid
Cerebellar Syndrome	Paraparesis
Cerebral Artery Embolism	Paraplegia
Cerebral Artery Occlusion	Paresis
Cerebral Artery Thrombosis	Partial Seizures
Cerebral Disorder	Post Procedural Complication
Cerebral Haemorrhage	Post Procedural Haemorrhage
Cerebral Hypoperfusion	Pupillary Reflex Impaired
Cerebral Infarction	Quadriplegia
Cerebral Ischaemia	Respiratory Arrest
Cerebral Thrombosis	Respiratory Failure
Cerebral Venous Thrombosis	Retinal Vein Occlusion
Cerebrovascular Accident	Sensorimotor Disorder
Clonic convulsion	Sensory Disturbance
Clonus	Sensory Loss
Coma	Simple Partial Seizures
Complex Partial Seizures	Spastic Paralysis
Convulsion	Spinal Artery Embolism
Cranial Nerve Paralysis	Spinal Claudication
Deafness Neurosensory	Spinal Cord Disorder
Diaphragmatic Paralysis	Spinal cord infarction
Embolic Stroke	Spinal Cord Injury
Embolism	Spinal Cord Ischaemia
Embolism Venous	Spinal Cord Oedema
Encephalopathy	Spinal Cord Paralysis
Facial Paresis	Spinal Disorder
Faecal Incontinence	Spinal Shock
Grand Mal Convulsion	Sudden Death
Haemorrhage	Thalamic Infarction
Haemorrhagic Cerebral Infarction	Thrombosis

Hemiparesis	Urinary Incontinence
Hemiplegia	Vascular Injury
Hyperaesthesia	Vascular Occlusion
Hyperkinesia	Vasogenic Cerebral Oedema
Hyperreflexia	Vasospasm
Hypoaesthesia	Venous Thrombosis
Hypoaesthesia Facial	Vertebral Artery Thrombosis
Hyporeflexia	Visual Impairment
Iatrogenic Injury	Wrong Technique In Drug Usage Process
Incontinence	

8.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.4 APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

FAERS Case #	Version	Manufacturer Control #	FAERS Case #	Version	Manufacturer Control #
3004479	1	3410/11757	8870948	1	
3014654	1	3426/11757	8919983	1	US-009507513-1211USA007279
3040402	1	3478/11757	8939941	1	US-009507513-1211USA011635
3122770	5	1998 USA 001491	8950800	1	
3232941	1	3615/11757	9062497	1	US-BRISTOL-MYERS SQUIBB COMPANY-17297656
3321485	4		9115608	1	US-BRISTOL-MYERS SQUIBB COMPANY-16349094
3518614	2	2000026706US	9122698	2	
3648962	1		9173619	2	
3727922	1	11052792	9185786	1	
3739005	2	2001083307US	9209610	1	
3739007	1	2001083311US	9325454	1	
3805182	1	2002109192US	9376344	1	US-BRISTOL-MYERS SQUIBB COMPANY-19033919
3813910	1	US-BRISTOL-MYERS SQUIBB COMPANY-11943305	9401487	1	US-PFIZER INC-2013202560
3853477	1	US-BRISTOL-MYERS SQUIBB COMPANY-12089553	9476670	1	US-BRISTOL-MYERS SQUIBB COMPANY-18914796
3855421	1		9476766	1	US-BRISTOL-MYERS SQUIBB COMPANY-18988675
3926989	1		9786955	1	US-ACTAVIS-2013-23589
3988555	1	US-BRISTOL-MYERS SQUIBB COMPANY-12353694	9797130	1	
4009004	1		3291891	1	2662/11757
4015256	1	US-BRISTOL-MYERS SQUIBB COMPANY-12340881	3441932	1	
4098351	1		3479641	1	2000015753US
4164262	6		3559887	1	
5651798	2	BDI-006523	3638378	1	2001-03-2105
5652134	1		3647211	1	2000-007
5676471	1	2004241269US	3779106	1	2002-03-1837
5703475	1	2004107918	3818055	1	2002096240US
5710755	1		3971022	1	
6788192	1	US-BRISTOL-MYERS SQUIBB COMPANY-14063028	4011691	1	
5809344	1	2005074300	4101343	1	2004199719US

FAERS Case #	Version	Manufacturer Control #	FAERS Case #	Version	Manufacturer Control #
5828195	1	2005087350	4105288	1	
5885939	3	2005AC01439	4105827	1	
5891282	1		4147002	1	
6006777	3	US-AVENTIS-200612355GDDC	4159776	1	
6115044	2	2006-BP-08760RO	4198690	1	2003166735US
6169797	1	2006SP000053	4422498	1	23944
6215391	1	2006153907	4424029	1	20771
6216466	1		4453425	1	20297
6337471	1	2217-138	4464454	1	1203
6338723	1	2217-140	4492155	1	132611757
6338902	1	2217-139	4499837	1	135711757
6361277	1		4500013	1	134611757
6499868	1	US-PFIZER INC-2007101421	4724117	1	190911757
6554178	7	US-BRISTOL-MYERS SQUIBB COMPANY-14063168	5658170	1	2004238364US
6579099	1	US-BRISTOL-MYERS SQUIBB COMPANY-14106041	5665200	1	
6613186	2	US-PFIZER INC-2008028987	5774086	1	
6811279	1	US-WATSON-2008-06598	5840365	1	US-BRISTOL-MYERS SQUIBB COMPANY-13030820
7044612	1		5840895	1	2004238434US
7045611	1	299482	5890915	1	
7125604	1	US-TEVA-209613USA	5908755	1	2005-10-0383
5996937	1	2006019308	5937731	2	US-PFIZER INC-2007064879
5920510	1	2005145684	5942635	1	2005160909
6108136	2	2006091892	6108141	1	
6432120	1	US-PFIZER INC-2002105646US	6160837	1	2006SP003889
6815339	1	US-BRISTOL-MYERS SQUIBB COMPANY-14409635	6241744	1	US-PFIZER INC-2006002584
7156964	1	US-BRISTOL-MYERS SQUIBB COMPANY-14666200	6384685	1	2006089484
7195121	3	US-ASTRAZENECA-2009SE29022	6384690	1	2006135757
7255317	1	US-PFIZER INC-2010005547	6602927	1	
7257963	1	2010SP001548	7243120	2	
7318719	1	US-PFIZER INC-2010029782	7515346	1	US-PFIZER INC-2006089484
7364670	1	US-PFIZER INC-2010045744	8280040	1	190911757
7409256	1		8281867	1	202111757
7515484	2	US-PFIZER INC-2005156051	8430450	1	US-PFIZER INC-2012046364

FAERS Case #	Version	Manufacturer Control #	FAERS Case #	Version	Manufacturer Control #
7576635	1	US-BRISTOL-MYERS SQUIBB COMPANY-15263346	9034344	1	
7605384	1	US-BRISTOL-MYERS SQUIBB COMPANY-15296411	9357945	12	
7637398	1	US-BRISTOL-MYERS SQUIBB COMPANY-15342090	9618959	1	US-PFIZER INC-2013291128
7953999	1	20110314	9619664	1	US-PFIZER INC-2013291130
7961428	1	20110335	9619999	1	US-PFIZER INC-2013291384
7989601	2	FK201100906	9663854	1	
8030753	1		9959618	1	
8157767	1		10045580	1	US-PFIZER INC-2014087273
8349434	4	3391/11757	10040851	1	
8389359	1	US-PFIZER INC-2012026745	10065290	1	US-PFIZER INC-2014096244
8504409	1	US-BRISTOL-MYERS SQUIBB COMPANY-16496465	3026878	1	990/11757
8566940	1	2012SP024516	3644594	1	
8657668	1	US-BRISTOL-MYERS SQUIBB COMPANY-16728412	5679911	1	
8780124	2		3816307	1	2002113084US
8843376	1	US-PFIZER INC-2012252719	4211481	1	
8854098	4				

8.5 APPENDIX E. SUMMARY OF CASES SERIES

8.5.1 *Cases That Reported A Serious Neurological Adverse Event with a Fatal Outcome (n=3)*

Three cases reported an outcome of death:

FAERS Case # 3004479 – A 54-year-old female with a history of migraines and ischemic brain disease developed a massive ischemic cerebral vascular incident following a cervical epidural administration of methylprednisolone acetate, using fluoroscopy. The incident occurred at the end of the procedure. Magnetic resonance imaging (MRI) revealed a bilateral massive stroke. Quadriplegia resulted and respiratory support was required. The patient elected to terminate respiratory support later that month and subsequently died. Intraarterial administration of methylprednisolone was investigated as a possibility of the serious event.

FAERS Case # 6215391 – See Section 4.1 Selected Cases for a description of this case with methylprednisolone acetate use.

FAERS Case # 6338902 – A 48-year-old female with a history of C5-C6 herniated nucleus pulposus secondary to a motor vehicle accident 5 months prior and a C6 radiculopathy, experienced a massive cerebellar infarct and death following a cervical, transforaminal block with triamcinolone 80 mg. The patient was administered midazolam 2 mg, fentanyl 100 mcg, Isovue M 200 non-ionic contrast medium 2 ml, via epidurogram, confirming placement, and bupivacaine 0.25% 2 ml. The patient became unresponsive upon self-transfer from the table to the stretcher. She was intubated due to persistent unresponsiveness and inability to maintain adequate oxygenation. The patient regained consciousness 1 hour later and was able to follow commands. She was admitted to the neurological intensive care unit due to her complete loss of movement in her right arm, weakness in the left grip strength and minimal strength in the legs bilaterally. The patient underwent brain stem decompression surgery when focal neurological deficits were noted. The patient died the following day. Finding at operation were significant for an anomalous tortuous vertebral artery. Pathology revealed bilateral cerebellar infarction, left occipital cortex infarction, and thromboembolism in a leptomeningeal artery adjacent to the left occipital cortex.

8.5.1 *Cases That Reported A Serious Neurological Adverse Event with a Non-Fatal Outcome (N=87)*

Methylprednisolone (n=43)

Forty-three cases reported non-fatal serious neurologic adverse events occurred with methylprednisolone. Thirty-seven cases reported use with methylprednisolone acetate and the remaining six cases did not report which formulation of methylprednisolone was administered. The mean time to onset of adverse events was 15 days, with a range of within 1 day to 1 year. Twenty cases reported the dose of methylprednisolone, which ranged from 40 – 160 mg. The epidural route of administration was reported in six cases: transforaminal (n=2), interlaminar

(n=2), and caudal (n=2). Twelve cases reported fluoroscopy, CT, or a contrast agent was utilized during the procedure. Nineteen cases reported the location of ESI administration: cervical (n=8), cervical/thoracic (n=1), lumbar (n=7), lumbar/sacral (n=2), and sacral (n=1). The serious neurologic adverse events were reported as: spinal cord infarction, other infarctions (cerebellar), paralysis, stroke, coma, cerebellar artery thrombosis, blindness, hemorrhages of the eyes, meningitis, seizures, neuropathy (unspecified), cauda equina syndrome, muscle spasms, paresis, dysesthesia, dyskinesia, dysarthria, personality/behavioral changes, and urinary/bowel dysfunction. Four cases reported potential causes of the adverse events: one case reported the patient may have received the ESI as an intraarterial injection; a second case reported the patient received an intrathecal injection into the subarachnoid space prior to the epidural; a third case reported an attempted CESI was placed into the subdural space; and a fourth case reported that there is a difference in particulate aggregation properties of generic methylprednisolone in comparison to the Depo-Medrol formulation or Celestone which had been used in past injections. Twenty-eight cases reported an event outcome: continued (n=21) and resolving/resolved (n=7).

Triamcinolone (n=36)

Thirty-six cases reported non-fatal serious neurologic adverse events occurred with triamcinolone use. The mean time to onset of adverse events was within 1.6 days, with a range of within 1 day to 7 days. Twenty cases reported the dose of triamcinolone, which ranged from 40 – 120 mg. The epidural route of administration was reported in 13 cases: transforaminal (n=11) and interlaminar (n=2). Seventeen cases reported fluoroscopy, angiography, and/or contrast media was utilized during the procedure. Twenty-five cases reported the location of ESI administration: cervical (n=9), cervical/thoracic (n=2), cervical/lumbar (n=3), thoracic (n=1), thoracic/lumbar (n=1) and lumbar (n=9). The serious neurologic adverse events were reported as: spinal cord infarction, other infarctions (cerebellar), paralysis, thromboembolism, stroke, cardiac arrest, dysesthesia, paresis, transient blindness, neuropathy, muscle spasms, tremors, urinary/bowel dysfunction, syrinx, aphasia, and transient loss of consciousness. Four cases reported potential causes of the adverse events: one case reported the injection entered the patient's vein instead of epidural space; a second case reported iopamidol may have caused paraplegia and lower extremity paralysis, a third case reported a potential inadvertent intraarterial injection and the movement of the needle after the final injection of Isovue and before the injection of the steroid and local anaesthetic solution; and a fourth case reported several potential causes which included direct injury to the artery, vasospasm caused by the steroid or anesthetic, end-capillary occlusion by steroid particles and needle related factors (volume deformation or postcontrast needle movement). Twelve cases reported an event outcome: continued (n=10), resolving/resolved (n=2).

Betamethasone (n=3)

Three cases reported non-fatal serious neurologic adverse events with betamethasone use. One case reported a 58-year-old male experienced seizures, transient blindness, vertigo, muscle pain and weakness 1 month after receiving cervical interlaminar injection of betamethasone sodium phosphate (dose unknown) with fluoroscopy use for an unknown indication. No further information was provided. A second case reported a 63-year-old male experienced spinal cord infarction and paralysis after receiving a transforaminal lumbar injection of betamethasone

(formulation unknown) 12 mg and 1% lidocaine (epidurally) with fluoroscopy use for low back pain with radicular symptoms. Relevant medical history included previous ESIs without complications. The patient was discharged with power wheelchair mobility and required assistance for daily activities.¹⁷ A third case reported an 83-year-old female who experienced acute spinal cord infarction, paraplegia, and neurogenic bladder and bowel after receiving betamethasone acetate/sodium phosphate 6 mg with bupivacaine with fluoroscopy for radicular pain. Relevant concomitant medications included non-steroidal anti-inflammatory drugs (NSAIDs), gabapentin, and hydrocodone. Medical history was unknown, but the patient had no history of lower extremity numbness or weakness. She had partial motor recovery at the time of reporting.¹³

Dexamethasone (n=3)

Three cases reported non-fatal serious neurologic adverse events with dexamethasone use. One case reported a 30-year-old female experienced “new pain and numbness” and “new tingling in left leg” after receiving a lumbar/sacral injection of dexamethasone (dose unknown) for an unspecified condition. MRI (unspecified date) showed no change from baseline/previous MRI. The event outcome was unknown at the time of reporting. A second case reported a 50-year-old female experienced sudden neck pain, hypotension, headache, and a burning sensation in her neck, shoulder and legs after receiving a CESI with dexamethasone 10 mg. The patient’s medical history included chronic degenerative disease of c-spine and asthma. Concomitant medications include Omnipaque. MRI performed in ED revealed no acute changes. The patient recovered from the events. A third case reported an 89-year-old male who experienced numbness in the left leg, increased pain in both legs, and dizziness within 24 hours after receiving a lumbar injection of dexamethasone (dose unknown). Medical history included Parkinson’s disease, degenerative joint and disc disease of the lumbar spine, and radicular left leg pain. She was treated with a Medrol dose pack and at the time of reporting the outcome of the events was ongoing.

Hydrocortisone

There were no reports of serious neurologic adverse events with hydrocortisone use.

Epidural Steroid Injection unspecified (n=2)

Two cases reported non-fatal serious neurologic adverse events with ESI use, but did not identify the injectable steroid product. One case reported a 58-year-old (gender unknown) experienced blurred vision, numbness in extremities, dysesthesia, loss of bowel and bladder control, migraine headache and tremors in right hand after receiving an unknown ESI in his upper and lower back for an unknown indication. The event outcome was not resolved at the time of reporting. A second case reported an 88-year-old female experienced a migraine headache, increased blood pressure, new aches and pains, weight loss, anemia after receiving a second injection of an ESI. The event outcome was not reported and no further information was provided.

8.5.2 Cases That Reported Arachnoiditis and A Fatal Outcome (n=2)

FAERS Case # 10045580 – A 41-year-old male experienced severe adhesive arachnoiditis and death due to completed suicide after starting methylprednisolone acetate 320mg (8 lumbar/facet injections x 40mg) for minor lower back pain. Relevant medical history and relevant concomitant medication were unknown. Since an unknown time after the ESI procedure, the patient “was not able to endure the trauma and pain, he was not able to stand long enough to hold his own body weight, he was not in a good condition, he lost weight, his body decreased in size and diagnosed with neurological rash shortly after the procedure when he went to the emergency room due to an unspecified reason.” It was also reported that since an unknown date while on methylprednisolone acetate the patient experienced lack of physical abilities, severe pain, severe fibroids pain, and severe adhesive arachnoiditis. He committed suicide reportedly due to physical disabilities due to the ESI procedure. The patient did not recover from the adverse events at the time of death. An autopsy revealed the reason of death was suicide.

FAERS Case # 9619664 - A male patient, of unknown age, experienced arachnoiditis after receiving methylprednisolone acetate at an unknown dose and frequency for an unspecified indication. Relevant medical history and concomitant medications were unknown. It was reported that the patient committed suicide due to the diagnosis of arachnoiditis, which resulted in his death. Relevant lab data was unknown. It was unknown if autopsy was performed. The clinical outcome of arachnoiditis was not recovered.

8.5.3 Cases That Reported Arachnoiditis and A Non-Fatal Outcome (N=39)

Methylprednisolone (N=33)

Thirty-three cases reported arachnoiditis occurred with methylprednisolone use and a non-fatal outcome. Thirty-two cases reported use of methylprednisolone acetate and the remaining case did not report which formulation of methylprednisolone was used. The mean time to onset of arachnoiditis was 58.5 days, with a range of within 1 day to 1 year. Seven cases reported the dose of methylprednisolone, which was 80 mg. One case reported the epidural route of administration: interlaminar (n=1). One case reported that no imaging was used; one case reported a contrast agent was used; and the remaining cases did not report whether or not imaging or imaging agents were used. Five cases reported the location of ESI administration: lumbar (n=4), and sacral (n=1). Two cases reported concomitant bupivacaine was administered; one of these cases reported the anesthetic was given epidurally and the remaining case did not specify a route of administration. Fifteen cases reported the patient received prior ESIs. Fifteen cases reported an event outcome: continued (n=15). Two cases reported the patient may have received an inadvertent intrathecal injection instead of the intended epidural injection. One case reported the patient’s dura was punctured during the procedure. Examples of other neurologic adverse events reported with arachnoiditis included: paralysis, increased pain, neuropathy, depression, pain, urinary/bowel dysfunction, gait disturbance, vertigo, and headache.

Triamcinolone (N=4)

Four cases reported arachnoiditis occurred with triamcinolone use. One case reported a male patient (age unknown) experienced arachnoiditis after receiving triamcinolone (dose unknown) for an unknown indication. The outcome of the event was reported as disabled as the patient is dependent on a wheelchair for mobility. No further information was provided. A second case reported a 25-year old-male who experienced arachnoiditis after receiving triamcinolone epidurally and intrathecally (dose unknown) in the lumbar/sacral region for sciatica and a back injury. Concomitant medications administered included lidocaine and bupivacaine (route unknown). An event outcome was not reported. A third case reported a 43-year-old female patient experienced adhesive arachnoiditis after receiving triamcinolone (dose unknown) and bupivacaine (epidurally) for an unknown indication. She had a past medical history of discogenic disease of the lumbar spine. No further information was provided. A fourth case reported a 44-year-old male was diagnosed with arachnoiditis, cauda equina syndrome, stenosis and fibrosis after receiving a CESI with triamcinolone (Kenalog 80) without fluoroscopy for shoulder pain. The injection was given using the hanging drop technique. The event outcome was not reported and no further information was provided.

Betamethasone (N=2)

Two cases reported arachnoiditis occurred with betamethasone use. One case reported a 35-year-old female experienced burning back pain, “buzzing” in legs and feet and severe stabbing/shooting pains two weeks after receiving betamethasone (unknown formulation, unknown dose) with iohexol for an unknown indication. It was reported that the patient did not have a history of back surgery. The patient was diagnosed with adhesive arachnoiditis and no additional information was provided. The second case was a 52-year-old female who experienced arachnoiditis after receiving betamethasone acetate/betamethasone sodium phosphate (dose unknown) for an unknown indication. No additional information was provided.

8.6 APPENDIX F. ANNOTATED BIBLIOGRAPHY

8.6.1 *Cervical Injections*

1. Sadacharam K. et al. Inadvertent subdural injection during cervical transforaminal epidural steroid injection. *Case Rep Anesthesiol.* Epub 2013 Dec 31. This publication describes a case of a C5-6 transforaminal epidural steroid injection. Fluoroscopy revealed a subdural contrast pattern. In this instance, the needle was repositioned. No complications ensued. The authors contend: “The subdural space is a potential space between the arachnoid and dura mater... [Since it] is larger in the cervical region, there may be an elevated potential for inadvertent subdural injection. Needle placement in the cervical subdural space during transforaminal injection is uncommon. Failure to identify aberrant needle entry within the cervical subdural space may result in life threatening complications. We recommend initial injection of a limited volume of contrast agent....”

2. Fitzgerald RT et al. Vertebral artery position in the setting of cervical degenerative disease: implications for selective cervical transforaminal epidural injections. *Interv Neuroradiol.* 2013 Dec; 19(4):425-31. This article describes a study with the objective of assessing the position of the vertebral artery relative to the typical cervical transforaminal epidural injections. Using CT-fluoroscopy guidance, 68 patients had cervical TF injections (at 70 levels). The authors contend that “vertebral artery position is commonly displaced into the foramen in patients with advanced cervical degenerative disease.” Furthermore, the “needle trajectory intersected with the vertebral artery in 30 of 70 injections (46%) by CT-fluoroscopy.

3. Candido KD and Knezevic N. Cervical epidural steroid injections for the treatment of cervical spinal (neck) pain. *Curr Pain Headache Rep.* 2013. Feb; 17(2):314. This is an excellent comprehensive review and analysis of the literature. Authors contend that the evidence for efficacy is “weak” compared with that for lumbar injections. However, they cite one study (Lee et al. *Spine.* 2012) in which “80% of patients were able to avoid having discectomy or fusion surgery.”

In terms of complications, they acknowledge that “multiple cases of unintentional intra-arterial injection of corticosteroids and resultant spinal cord injuries have been reported even when using fluoroscopic guidance. “ In addition, “minor adverse events such as non-specific headache, nausea and vomiting, vasovagal reaction, facial flushing, transient lightheadedness, and transient paresthesias have been reported following both CTFESIs, and CILESIs. ... [One study] showed the incidence of all complications after CILESIs to be 16.8 %. However, there are many cases illustrating serious complications such as spinal cord or brainstem infarction, severe spinal cord injury, epidural hematoma, grand mal seizure, stroke, cardiopulmonary arrest, and death. The spinal infarction was speculated to be secondary to the unintentional intravascular injection of a “particulate” corticosteroid during CTFESI. Grand –mal seizures have been documented as transient ... Death usually occurs from massive cerebral edema secondary to dissection and perforation of the vertebral artery, while cardiopulmonary arrest was thought to occur ... [from] pneumocephalus...” Candido cites a study as showing that 19.4% of CTFESIs with fluoroscopy were associated with intravascular injection. He cites another study wherein 15.5% were thought

to be arterial injections. Further he suggests that intravascular injection of a “particulate” steroid can lead to thromboembolism and subsequent spinal or brainstem infarct. Detection of an intravascular injection via aspiration of blood in the needle is reported in one study to be only 45.9% sensitive.

Candido further discusses other imaging modalities such as CT, CT-fluoroscopy, ultrasound and digital subtraction angiography which could be used to minimize the chance of intra-arterial injection. He reports that “safety...of CT and CT-fluoroscopy guided CESIs . . . [was] reported in many studies... However, there was a singular report of needle puncture through the anterior spinal artery... under fluoroscopic guidance.” While he reports that digital subtraction angiography (DSA) may be useful he goes on to say that there is “insufficient evidence to support the efficacy and outcome of DSA role in CESIs and there is no guarantee that DSA will improve clinical outcomes or minimize complications.”

Regarding the use of blunt needles to minimize the chance of intravascular penetration, he cites evidence (including a case report he authored) that blunt needles “may not be protective.” In discussing the type of steroid used in an ESI, Candido states that “non-particulate steroids may be safer...” But “of the non-particulate corticosteroids dexamethasone is the only steroid that has not yet been implicated in spinal cord or brainstem infarction following CESIs.”

Candido concludes with the statement that “these injections carry the risk of complications” and suggests that to reduce the risk one should use: real-time fluoroscopy, CT, CT-fluoroscopic guidance or DSA, test doses of local anesthetics, only “non-particulate” steroids, and blunt needles.

4. Cohen-Adad J et al. Cervical spinal cord injection of epidural corticosteroids: comprehensive longitudinal study including multiparametric MRI. *Pain*. 2012 Nov;153(11):2292-9. This paper describes a case of intramedullary injection during interlaminar ESI. The patient, a young woman with neck pain and headache received two interlaminar cervical ESIs. After the second she developed a left hemiparesis and sensory loss that persisted through her examination at 28 months post injection. The authors describe an experimental MRI technique used to follow her pathology longitudinally. They also relate that a literature search conducted in 2011 revealed a “dozen published cases of cervical-SCI [spinal cord injury] after interlaminar approach to cervical-ESI.” They note that “serious complications include two epidural abscesses....one subdural hematoma, with outcomes ranging between full recovery to paraplegia.” They also identify “3 prior cases of injection into or through the cervical cord during cervical-ESI; one from transforaminal approach and two from interlaminar approach....” Authors also note that “two prospective and a half-dozen retrospective studies (vide infra) find complications rare but relatively more frequent after cervical than lumbar epidural-steroid injection.”

5. Popescu, A. et al. Stroke following epidural injections – Case report and review of literature. *J Neuroimaging*. 2013 Jan;23(1):118-21. This is a case report of a 66 year old female who underwent transforaminal CESI for pain. Fluoroscopy was used; there was no blood on needle drawback, and methylprednisolone acetate was injected. She developed flaccid quadriplegia within 45 minutes and at 3 weeks remained in this condition. MRI showed edema and confirmed a cord infarction. This case prompted a literature review which identified 15 additional cases of

spinal cord and posterior circulation ischemia. Of the 16 cases, two exhibited transient symptoms, 10 had long term sequelae, and 4 patients died. Death and serious sequelae occurred despite the use of fluoroscopy and the absence of blood on needle drawback. Also, posterior placement of the needle did not preclude a bad outcome. While not all intravascular injections result in infarct, Popescu cites a study of 504 transforaminal cervical injections with a 19.4% rate of intravascular injection despite the use of fluoroscopy. Additionally, though many of the cases did not report the type of steroid used, one case with MRI confirmation of a cerebellar and cervical cord infarct was associated with the “non-particulate” steroid betamethasone.

6. Tiso, R et al. Adverse central nervous system sequelae after selective transforaminal block: the role of corticosteroids. *The Spine Journal* 4 (2004) 468-474. This paper describes a case of acute cerebellar infarction followed by death after a cervical transforaminal injection with Triamcinolone, a “particulate” steroid. Direct fluoroscopy was used to visualize the neural foramen. The patient was conscious throughout the procedure and remained stable throughout the procedure. In reviewing different types of steroids he states: “the sodium phosphate moiety renders the steroidal compound water soluble in the case of betamethasone and dexamethasone, rendering both appropriate for parenteral use ... and possibly safer in the event of inadvertent intravascular injection” He also states: “Particulate size ... may play a role their use should be reevaluated.” Yet, he concludes “there are no studies advocating one corticosteroid formulation over another for safety. Similarly there are no good clinical outcome studies comparing one method of epidural administration over another ... the practice of epidural corticosteroid administration requires further study.

8.6.2 Lumbar Injections

7. Ghai, B et al. Transforaminal vs parasagittal interlaminar epidural steroid injection in low back pain with radicular pain: a randomized double-blind active-control trial. *Pain Physician*. 2014 Jul-Aug; 17(4):277-90. Transforaminal is generally considered more efficacious than interlaminar because of better ventral epidural spread. But “catastrophic complications reported with the TF approach have raised concerns regarding its use.” These concerns led to a search for an alternative approach. The parasagittal interlaminar route (PIL) is supposed to have good ventral spread; this study compares the efficacy of IL and TF approaches. The study involves 62 patients randomized to receive fluoroscopically guided injection of methylprednisolone via either the PIL (n=32) or TF (n = 30) approach. Efficacy is about the same; over 75% had more than 50% pain relief by VAS. No complications are reported in either group, but 3 patients had intravascular spread of contrast in the TF group.

8. Hong J et al. Comparison between digital subtraction angiography and real-time fluoroscopy to detect intravascular injection during lumbar transforaminal epidural injections. *Reg Anesth Pain Med*. 2014 Jul-Aug;39(4):329-32. This paper describes a comparison of digital subtraction angiography and real-time fluoroscopy to detect intravascular injection during lumbar transforaminal epidural injections. “Infrequent but serious complications of transforaminal epidural steroid injection (TFESI) are thought to be due to inadvertent intravascular injection (embolization of corticosteroid particulates via the vertebral or thoracolumbar radiculomedullary arteries).” This article reviews 239 patients with 249 TF injections all involving the classic

technique by one physician. Overall, 12.4% were associated with intravascular injection. Fluoroscopy failed to detect 9 cases that were detected by DSA, so DSA may be a better imaging modality.

9. Ilkhchoui Y and Koshkin E. A blunt needle does not eliminate the risk of vascular penetration during transforaminal epidural injection. *Surg Neurol Int.* 2013. Oct 29;4(suppl 5): S404-6. This article describes a 59 YO F who underwent TFESI at L5-S1 with a blunt needle but still experienced an intravascular injection. When this was noted, the needle was repositioned until contrast spread along the nerve root and epidural canal. Steroid was then administered and no complications ensued. The authors report a 9-26% risk of vascular injection in fluoroscopy-guided TFESIs, incidence depending on the site. The authors also report at least 4 cases of spinal cord injury and paraplegia from intra-arterial injection into the arteries of Adamkiewicz. Use of blunt tip needle has been suggested as a tool to reduce risk, but that was used here and the patient still experienced intravascular penetration. The authors contend that that live fluoroscopy is critical.

10. Hong JH et al. Analysis of inadvertent intradiscal and intravascular injection during lumbar transforaminal epidural steroid injections: a prospective study. *Reg Anesth Pain Med.* 2013 Nov-Dec; 38(6):520-5. This study evaluates 251 TFESIs in 219 pts. The needle position was confirmed with fluoroscopy (biplanar), then, contrast was injected. They proceeded to assess the incidence of intradiscal injection, blood flashback and intravascular spread using static and real-time fluoroscopy. Intradiscal injections occurred in 6 patients (2.3%). Intravascular injections were seen in 39 patients (15.5%). The sensitivities for detecting intravascular access via aspiration or static fluoroscopy with contrast were 20.5 and 51.2% respectively. Therefore, inadvertent intradiscal and intravascular injection are not rare. The aspiration test and static fluoroscopy often fail to detect. Real time fluoroscopy should be the gold standard, contend the authors.

11. DePalma MJ et al. Corticosteroid choice for epidural injections. *PM R.* 2013. Jun;5(6):524-32. This publication summarizes a debate between two doctors, and commentary by a third, about the pros and cons of “particulate” compared with non-particulate steroids. They present a case and discuss the pros and cons of a repeat transforaminal injection (lumbar spine) with or without “particulate” steroids. DePalma argues in favor of use of a “particulate” preparation in the TFESI asserting that it has greater (known) efficacy; he states: “No studies that assessed TFESIs in LSS have been published that used a “non-particulate” steroid preparation.” He further argues that “safeguards can be exercised to reduce the risk....” Alison Stout argues that “a large proportion of these [CNS] injuries during the transforaminal approach have been attributed to occlusion of an artery that supplies the central nervous system. Specifically, this complication is thought to arise from the injection of a “particulate” corticosteroid into a radiulomedullary or vertebral artery, which results in an embolic injury and causes permanent and catastrophic ischemic injury to the spinal cord and brain.” Stout cites evidence (some based upon animal studies) to support her point of view.

12. Sawhney M. Lumbar epidural injections for low back pain. *Nurse Pract.* 2013. Jul 10;38(7):11-2. This article describes “how to” perform an ESI. There are 3 approaches: transforaminal, caudal, and interlaminar. She also gives percentages for AEs. She contends that

this type of injection has recently been in the news because of an outbreak of fungal meningitis caused by contaminated products. Yet, the most common adverse reaction experienced after an ESI is a vasovagal reaction (8.7%) leading to hypotension, nausea, and vomiting. Other complications include intravascular injection (7.2% to 22%), headache (3%), dural puncture, infection, or hematoma. Some patients experience increased back pain (2.4% to 5%) after the injection and until the medications take effect. Other potential adverse reactions include pain at the injection site, facial flushing, and transient erectile dysfunction of unknown etiology.

13. Park Y et al. Ultrasound-guided vs fluoroscopy-guided caudal epidural steroid injection for the treatment of unilateral lower lumbar radicular pain: a prospective, randomized single-blind clinical study. 2013. The study randomizes 55 subjects to each of two arms. Efficacy/patient satisfaction was equivalent in both arms (up to 12 weeks). There were two intravascular injections (3.6%) with fluoroscopy, none with ultrasound. The authors argue for ultrasound in light of reduced exposure to radiation.

14. Ghai B et al. Lateral parasagittal versus midline interlaminar lumbar epidural steroid injection for management of low back pain with lumbosacral radicular pain: a double-blind, randomized study. *Anesth Analg*. 2013. Jul;117(1):219-27. This is a double-blind, randomized study involving 37 patients randomized to receive either a parasagittal interlaminar (PIL) or a midline interlaminar (MIL) approach. "The transforaminal route is reported to be more effective than the interlaminar route due to higher delivery of drug at the ventral epidural space. However, the transforaminal route has been associated with serious complications including spinal cord injury and permanent paralysis. Hence, there is a search for a technically better route with fewer complications for drug delivery into the ventral epidural space. Recently, a parasagittal interlaminar (PIL) approach of epidural contrast injection was reported to have 100% ventral epidural spread. However, the therapeutic efficacy of this route has never been investigated." The authors conclude: PILs are more efficacious than MILs.

- a. Chen B. et al. Safety of Interlaminar and Transforaminal Epidural Steroid Injections. *Anesth Analg*. 2014. Jan;118(1): 236-7. Comment on Ghai et al. "we...disagree with the ...opinion that the parasagittal interlaminar approach may be safer than the approach following traditional TFESIs. At least 3 cases of lumbar paraplegia have been reported after interlaminar lumbar epidural steroid injections. The proposed mechanism is similar to that for paraplegia from a lumbar TFESI in which the epidural needle injured or penetrated the radiculomedullary artery and "particulate" corticosteroid was injected into the spinal canal with resultant spinal cord embolism and subsequent paraplegia." Chen then goes on to describe the anatomy of the radiculomedullary artery (Adamkiewicz artery) and concludes that "neither midline nor parasagittal interlaminar lumbar epidural steroid injections are completely risk-free with respect to potential needle vascular injury and paraplegia, particularly if particulate corticosteroids are used...."
- b. Ghai B. et al. In response (to Chen). "We agree with Chen et al. that neither midline interlaminar nor parasagittal interlaminar approaches of epidural steroid injections are completely risk free with respect to potential needle

related vascular injury because of wide variation of spinal vascular anatomy.”
 “What we implied in our article was that transforaminal epidural steroid injection is associated with higher incidence of catastrophic complication, and this is supported by literature. At least 18 cases of severe neurological damage and permanent paralysis are reported subsequent to transforaminal epidural steroid injection as compared with only 3 cases of paraplegia after laminar epidural steroid injection ...the overall rate of intravascular injection with lumbosacral transforaminal epidural steroid injection is reported to be 11.2% as compared with 1.2% after interlaminar epidural injection.”

15. Paik. Cauda equine syndrome caused by epidural pneumorrhachis; treatment with percutaneous computed tomography-guided translaminar trephination. *Spine*. 2013. Apr 1;38(7). This is a case report of pneumorrhachis (air in the epidural or subarachnoid space) causing cauda equine syndrome after a number of caudal injections. During 8 weeks following CT-guided translaminar trephination, the symptoms resolved; two years later the patient was symptom free.

16. Chang Chien GC et al. Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. *Pain Physician*. 2012. Nov-Dec;15(6):515-23. Chang Chien describes a case of “instantaneous and irreversible paraplegia following lumbar TFESI wherein a local anesthetic test dose, as well as DSA were used as adjuncts to fluoroscopy.” Patient was an 80 year old man who had previously undergone interlaminar injections. For this injection, aspiration revealed no blood or CSF. DSA was performed twice and a lidocaine test dose was administered without sequelae. However, after the injection with triamcinolone acetonide the patient immediately started experiencing pain, weakness, and numbness. He was subsequently diagnosed with paraplegia from an acute spinal cord infarction. He was discharged to a rehabilitation program with bilateral lower extremity paralysis and incontinence of bowel and bladder.

17. Hong JH et al. Analysis of Inadvertent Intradiscal Injections during Lumbar epidural Injection. *Korean J Pain*. 2014. Apr;27(2):168-73. This article describes a prospective study to evaluate the incidence of intradiscal (ID) injection during lumbar TFESI. Among the 249 TFESIs, 6 ID injections (incidence of 2.4%) were identified. ID injection carries the risk of developing diskitis.

18. Kim D and Brown J. Efficacy and Safety of Lumbar Epidural Dexamethasone versus Methylprednisolone in the Treatment of Lumbar Radiculopathy. *Clin/Pain*. 2011. July /Aug; 27(6): 518-22. This paper describes a study in which 60 patients were randomized to either methylprednisolone acetate (“particulate” steroid) or dexamethasone (“non-particulate” steroid). The goal was to compare efficacy and safety. All patients underwent translaminar lumbar epidurals. Though there were some differences in various efficacy measures none were statistically significant. There were no complications in either group. Kim states: “This study reconfirms the animal studies with no clinical neurotoxicity noted despite 1 intrathecal injection of DP [dexamethasone] ... the small numbers in this study receiving DP does limit any definitive conclusions about the safety of routine use of epidural DP.”

8.6.3 Lumbar, Cervical, Thoracic Injections

19. Cohen SP et al. Epidural steroids: a comprehensive evidence-based review. *Reg Anesth Pain Med.* 2013. May-Jun;38(3):175-200. Excellent summary of studies in literature. The first therapeutic epidural performed in 1885 on a human was to treat “seminal incontinence” and “addiction to masturbation.” In 1901, this technique was first used to treat radicular pain with the injection of dilute solutions of cocaine...” The first part of the publication reviews studies vis-à-vis efficacy. The second part reviews studies providing information about complications. Regarding neurotoxicity, he contends: “Direct neurotoxicity... has been hypothesized to result in arachnoiditis and aseptic meningitis... However, the link ... is not at all clear...The reported cases of arachnoiditis were associated with multiple intrathecal injections, and in most cases there was preexisting neurologic disease. Arachnoiditis and aseptic meningitis are complications of intrathecal, not epidural injections. The use of a local anesthetic test dose and/or fluoroscopy... [can] prevent intrathecal administration.” Regarding neurologic injury he relies upon a study of malpractice claims (Closed Claims Study) conducted by the American Society of Anesthesiologists; he states that “direct trauma to the spinal cord occurred in association with both the TF and IL routes.” And, “another mechanism of injury is the injection of steroid suspension into a spinal medullary artery with embolization of end arterioles supplying the spinal cord.” Cohen contends that the “Closed Claims analysis clearly demonstrates that injury to the cord is a significant risk for cervical, thoracic, and upper lumbar epidural injections.” He also states: “Catastrophic neurologic injury due to embolization of particulate steroid appears to be most common in association with cervical TF injection.” He concludes: “in summary, serious complications from injection of corticosteroid suspensions in to the epidural space are uncommon, but complications can be devastating ...the risks associated with the TF administration of depo-steroids in the upper lumbar, thoracic, and cervical regions preclude their use as a first line treatment.”

20. Lee HI et al. Transient adverse neurologic effects of spinal pain blocks. *J Korean Neurosurg Soc.* 2012. Sep;52(3):228-33. This publication summarizes a retrospective record review of 704 procedures (244 in the cervical spine and 460 in the lumbar spine) in 613 patients who received medial branch blocks (488), interlaminar epidural blocks (17) or transforaminal epidural blocks (199) between Dec 2009 and Jan 2011. The same three physicians performed the procedures which included a mixture of mepivacaine and triamcinolone acetonide. (During the last six months of the study a more dilute form of mepivacaine was used.) “Besides the well-known complications that may be permanent or fatal, transient adverse neurologic events....are encountered frequently. Although they are temporary, they are troublesome....” Ten patients had transient neurologic (and other) events including respiratory failure, quadriplegia, paraplegia, leg weakness.....all except one recovered within hours; the single exception recovered in two months.

21. Epstein NE. The risks of epidural transforaminal steroid injections in the Spine: Commentary and a comprehensive review of the literature. *Surg Neurol Int.* 2013 Mar 22;4(Suppl 2): S74-93. This is a broad literature review that includes published articles describing infections, neurologic events, efficacy of ESIs, adverse events associated with

epidural anesthesia, etc. It is useful because it is wide ranging and cites studies describing a variety of adverse events.

8.6.4 Animal study informative about the safety of steroid preparations.

22. Okubadejo G et al. Perils of Intravascular Methylprednisolone Injection into the Vertebral Artery. J bone Joint Surg Am. 2008;90:1932-8. This paper describes a study in which 11 pigs underwent deliberate injection (under fluoroscopic guidance) of the vertebral artery. Four animals were injected with a “particulate” steroid preparation (methylprednisolone acetate); seven were injected with “non-particulate” preparations (dexamethasone sodium phosphate and prednisolone sodium succinate). All four animals receiving “particulate” steroids failed to recover and required ventilator support after the procedure. The remaining seven recovered fully and demonstrated no evidence of neurologic injury.

8.6.5 Study of Arachnoiditis

23. Nanjayan SK et al. Arachnoiditis following caudal epidural injections for the lumbo-sacral radicular pain. Asian Spine J. 2013 Dec;7(4):355-8. This paper describes a case of arachnoiditis following caudal epidural steroid injections for lumbar radiculopathy. A few days after injection the patient presented with contralateral sciatica, worsening back pain, and urinary retention. These symptoms were followed by diminished motor function in the L4/L5/S1 myotome and foot drop. MRI suggested infective arachnoiditis.

8.6.6 Additional articles retrieved which may be informative overall but do not directly inform about the association between ESIs and serious neurologic adverse events.

24. Manchikanti, L et al. Epidural steroid warning controversy still dogging FDA. Pain Physician. 2014 Jul-Aug; 17(4): E 451-74. Criticizes FDA warning letter issued April, 2014. Contends that alternate techniques (e.g. avoidance of “particulate” steroids, use of a blunt needle, etc.) are not discussed. Acknowledges risk of spinal infarction, paralysis and death from cervical/thoracic transforaminal steroid injections, however author contends it is incorrect to extrapolate to all steroid injections and different types of epidurals (i.e. interlaminar or caudal). The author would like FDA to modify its statement to one “emphasizing the off-label use of epidural steroids which can cause rare, but serious neurologic problems following cervical and thoracic transforaminal epidural injections and also an increased risk with lumbar transforaminal epidural injections when performed without appropriate precautions.”

25. Manchikanti, 2014, Randomized Trial of epidural Injections for Spinal Stenosis Published in The New England Journal of Medicine: Further Confusion without Clarification. The author contends that data presented in the NEJM publication are misinterpreted and misleading.

26. Friedly, JL et al. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *NEJM* 2014 Jul 3;371(1):11-21. In this trial, 400 patients are randomized to epidural injections with steroids + lidocaine vs lidocaine alone. At 6 weeks there is no difference in efficacy. The approach (which did not appear to matter in terms of efficacy) included both interlaminar and transforaminal routes. AEs were higher in the steroid/lidocaine group than in the lidocaine-only group. And AEs were higher among patients with the transforaminal route. There were some intergroup differences: TFESIs with steroids vs TFESIs without steroids showed no advantage at 3 or 6 weeks. For the IL injections: those receiving steroids were improved at 3 weeks but the difference was minimal and not present at 6 weeks. Patients in both groups had decreased pain and improved function. The authors conclude that lidocaine alone is as good as steroids plus lidocaine.

27. Shamliyan, TA et al. Epidural steroid injections for radicular lumbosacral pain: a systematic review. *Phys Med Rehabil Clin N Am.* 2014 May;25(2): 471-89. This systematic literature review was based on 769 references including 15 publications of guidelines. It concludes there is no consistent evidence for sustained benefits from ESIs: "Reviews provided conflicting conclusions." The Cochrane Collaboration found no important benefit; the American Society of Interventional Pain Physicians found good benefit both short and long-term; other reviews found short-term, but not long term benefits (i.e. > 12 weeks). The authors contend the benefit of steroids is small and no better than an anesthetic alone. The authors also contend that different steroids are similar, and no single injection technique (transforaminal/caudal/interlaminar) improved back pain. They further argue that there is no conclusive evidence that a series of epidurals is more effective than a single injection. Complications are uncommon but the risk of contamination and infection is high. Routine off label use of epidural steroids for radicular lumbosacral pain is not recommended in this publication.

28. Lee SB et al. Bilateral central serous chorioretinopathy following epidural steroid injection. *Indian J Ophthalmology.*2013;61(9):514-5. This publication reports a single case of central serous chorioretinopathy after four epidural steroid injections for lower back pain.

29. Harris, Ian and Buchbinder, Rachelle. Time to reconsider steroid injections in the spine? *Med J Aust/* 2013. Aug 19; 199(4). The authors conclude: "Steroid injections to the spine provide no advantage over placebo, but do carry risks of harm."

30. Bellini M and Barbieri M. Systemic effects of epidural steroid injections. *Anaesthesiol Intensive Ther.* 2013. Apr-Jun; 45(2): 93-8. This literature review largely summarizes metabolic effects, not catastrophic ones.

31. Suh-Burghmann. Abnormal vaginal bleeding after epidural steroid injection: a paired observation cohort study. 2013. This article demonstrates that abnormal vaginal bleeding is a potential adverse effect (201 of 8166 procedures were followed by bleeding).

32. Mandel S et al. A retrospective analysis of vertebral body fractures following epidural steroid injections. *J Bone Joint Surg Am.* 2013. Jun 5;95(11):961-4. This is a case control study comparing 3000 patients who underwent ESI with 3000 matched controls. Those with ESIs had

a higher risk of vertebral fracture and authors suggest this is a result from weakening of bones from steroids.

33. Desai MJ and Dua S. Perineural hematoma following lumbar transforaminal steroid injection causing acute-on-chronic lumbar radiculopathy: a case report. *Pain Pract.* 2014.Mar;14(3):27107. This is a case report of a patient who developed progressive lower extremity weakness, sensory loss and ambulatory dysfunction during the week following a TFESI in the L3/L4 region. A contrast enhanced MRI revealed a small hematoma. Within two months the symptoms resolved.

34. Radcliff K et al. Epidural steroid injections are associated with less improvement in the treatment of lumbar spinal stenosis: A subgroup analysis of the SPORT. *Spine.* 2013.Feb 15;38(4):279-91. This study compares two (non-randomized) groups: those with and without an ESI at the outset of a four year study period. There was less improvement in the ESI group whether treated surgically or not over the study period. The authors report that the “results suggest ESI is associated with worse outcome in the treatment of spinal stenosis.” Though this is a negative efficacy study it is limited by its design: subjects were not randomized to the treatment arms and therefore there may be an unknown confounder affecting results.

35. Livingston EH and Lynm C. JAMA patient page. Steroid injections to treat back pain. *JAMA.* 2012. Nov 21;308(19):2047. This patient advice page from a major medical journal describes, pictorially, an epidural injection and provides advice about these. It advises that: “back injections with steroids and medications that numb nerves may provide short-term pain relief when a nerve is compressed.” It further advises that these should only be done for “nerve-related pain” and that “pain relief is short, lasting only a few weeks.” Finally it advises not to have more than 3 injections in a year as “beyond the first few injections, no further benefit from these injections is likely.”

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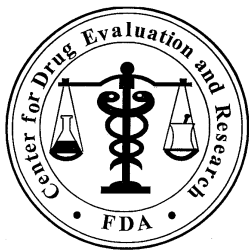
TARA L ARGUAL
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TARA L ARGUAL on behalf of SARA L CAMILLI
10/29/2014

JANE L GILBERT
10/29/2014

ALLEN D BRINKER
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SCOTT E PROESTEL
10/29/2014



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 5/14/2010

To: Badrul Chowdhury, MD, Director
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Subject: Catastrophic Neurologic Outcome after Transforaminal Epidural
Steroid Injection

Drug Name(s): Steroid Injections (betamethasone, dexamethasone,
hydrocortisone, methyprednisolone, and triamcinolone)

Application Type/Number and Applicant/Sponsor NDA 14-602 (Schering); ANDA 40-572, 40-491, 84-916, 87-702,
84-282, 87-440, 81-125 (Baxter, Luitpold); NDA 9-866
(Pharmacia and Upjohn); NDA 11-757 (Pharmacia and Upjohn);
NDA 12-041, 14-901, 16-466, 12-802, 11-685 (Apothecon,
Sandoz)

OSE RCM #: 2009-2228

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EXECUTIVE SUMMARY

This review evaluates the Adverse Event Reporting System (AERS) database and the relevant literature for the occurrence of catastrophic neurologic events reported after transforaminal epidural steroid injections for treatment of neck and back pain.

Specifically, this review focuses on three particulate steroids (hydrocortisone, methylprednisolone, triamcinolone) and two non-particulate steroids (betamethasone, dexamethasone). The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) requested a review to determine if a safety communication is needed.

Our findings in the AERS and literature data suggest catastrophic neurologic events such as spinal cord infarction or quadraplegia including fatal outcomes are associated with transforaminal epidural injections of particulate or non-particulate corticosteroid products. The Division of Pharmacovigilance II (DPV II) recommends a drug safety communication that warns of potential neurologic complications after transforaminal epidural particulate and non-particulate corticosteroid injections.

1 BACKGROUND

1.1 INTRODUCTION

DPARP has requested AERS and literature reviews of catastrophic neurologic events associated with transforaminal epidural steroid injections for treatment of back pain exclusive of other indications such as chemotherapy. The basis of this request was a concern raised by an outside pain physician who cited the potential for catastrophic events in this setting. At preliminary discussions, DPV II and DPARP agreed to restrict the assessment to epidural steroid injections used for radiculopathy-related back and neck pain. Such epidural procedures are currently unlabeled for injectable steroids. Catastrophic neurologic events after steroid injections have been reported, including spinal cord infarction, quadraplegia, cortical blindness, and fatal strokes.¹ This review is strictly limited to a safety assessment using AERS reports and literature review for case reports or case series; no efficacy assessment is made.

The transforaminal epidural technique uses a needle that is inserted through the posterolateral aspect of the intervertebral foramen. The intent is to deposit the drug in high concentrations adjacent to the affected spinal nerve at the site of inflammation. The categories of injectable corticosteroids are either particulate or nonparticulate based on its solubility and particle size (Table 4).

2 REGULATORY HISTORY

2.1 PRODUCT LABELING

No steroid preparation has a marketing indication for transforaminal epidural steroid injections for treatment of back pain; however, literature indicates the procedure has been used since at least 1961.

Depo-Medrol Sterile Aqueous Suspension (NDA 11-757) is specifically contraindicated for intrathecal administration based on reports of arachnoiditis following such administration. This contraindication is not mentioned in the labeling for celestone, dexamethasone, triamcinolone, or hydrocortisone (See Table 5 for approved products).

CONTRAINDICATIONS

Depo-Medrol Sterile Aqueous Suspension is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

Corticosteroid Preparations²

Most corticosteroid preparations contain corticosteroid esters, which are highly insoluble (i.e. particulate) in water forming microcrystalline suspensions. Particulate corticosteroid preparations in this case series includes methylprednisolone, triamcinolone, and hydrocortisone used for injections. Ester containing formulations have a larger particle size.

Dexamethasone and betamethasoneⁱ (sodium phosphate) are nonester corticosteroid formulations which are freely soluble (i.e. nonparticulate) in water. Nonparticulate formulations have a faster onset of action and may have a shorter duration of action relative to particulate formulations.

3 METHODS AND MATERIALS

3.1 AERS SELECTION OF CASES

The AERS database was searched on 12/23/2009 from approval dates for each of five steroid products for injection: betamethasone, dexamethasone, hydrocortisone, methylprednisolone, and triamcinolone for U.S. adverse event reports using the selected MedDRA preferred terms (Table 6). The preferred terms were chosen in agreement with DPARP to capture the events of interest (e.g. stroke, spinal cord infarction, quadriplegia,

ⁱ Celestone Soluspan contains a combination of betamethasone ester and betamethasone salt which may provide a dual action of quick onset and longer duration. Most clinical studies have not shown a significant difference between Celestone Soluspan and other corticosteroid ester preparations.

etc.). A total of 1,022 AERS reportsⁱⁱ were retrieved for the five steroid products.

Inclusion Criteria:

For the purpose of this review, we included cases that met the following criteria:

1. *Route of administration: epidural, “nerve block”, transforaminal, intravascular, intra-arterial, spinal injections*
2. *Neurologic Adverse event that persisted for greater than 24 hrs or no recovery at time of report*
3. *Permanent disability diagnosed by a physician shortly after spinal injections with corticosteroid preparations for back related pain*

We evaluated a sample of 248 reports from 1022 initial AERS reports that included all five steroid products. After our evaluation, we identified a total of 21 AERS cases out of 248 that met the inclusion criteria: methylprednisolone (8), triamcinolone (7), betamethasone (4), and dexamethasone (2). There were no cases of catastrophic neurologic adverse events associated with hydrocortisone injections (Table 7).

3.2 LITERATURE SEARCH

We performed a literature review consisting of PubMed searches performed on December 17, 2009 and January 27, 2010. PubMed search terms included combinations of the following terms: epidural, cervical, lumbar, sacral, lumbo-sacral, spinal, para-spinal, adverse event, catastrophe, catastrophic, death, stroke, paralysis, steroid, corticosteroid, gluco-corticoid, betamethasone, dexamethasone, cortisone, hydrocortisone, methylprednisolone, and triamcinolone.

4 RESULTS

4.1 AERS CASES

This reviewⁱⁱⁱ includes a detailed analysis of cases citing catastrophic neurologic events after injection with particulate (methylprednisolone, triamcinolone) and nonparticulate (betamethasone, dexamethasone) corticosteroids.

ⁱⁱ Original AERS Data Retrieved (Total N=1441) : Betamethasone (55), Dexamethasone (489), Hydrocortisone (130), Triamcinolone (171), Methylprednisolone (600). 1st Cut (excluded non-epidural from route of administration column in excel spread sheet: N= 419 leaving 1022 for sampling process)

ⁱⁱⁱ No cases meeting the inclusion criteria were identified for hydrocortisone injections.

The demographic characteristics and other parameters of particulate and non-particulate products are described, respectively, in Tables 1 and 2 below.

Table 1. Characteristics of catastrophic neurological events of AERS cases (U.S.) associated with methylprednisolone and triamcinolone as of 12/23/2009		
Parameter	Methylprednisolone N=8	Triamcinolone N=7
Gender	n=7 Male (3), Female (4)	n=6 Male (2), Female (4)
Age in years	n=6 Mean (47), Median (43) Range: 27 to 66 yrs	n=6 Mean (60), Median (56) Range: 48 to 71 yrs
Reported indication	n=5 Back pain (3), cervical spondylitis, (1), neck pain (1), post herpetic neuralgia (1)	Back/cervical pain (4), intervertebral disc herniation/tear (3)
Dose	n=4 20 mg (1), 40 mg (2), 120 mg (1)	n=2 40 mg, 80 mg
Route of administration	n=6 CESI (3), intraarterial ^{iv} (3), nerve block (1), intrathecal (1).	n=6 Transforaminal epidural (3), epidural (2), spinal (1)
Main adverse event ⁱⁱⁱ	Brain stem infarction (3), Stroke (2), Seizures (2), Massive brain edema (1) Paraplegia (1), Quadraplegia (1)	Paralysis (2), spinal cord infarction/ischemia (3), cerebellar infarction (1), paresthesia (1)
Estimated time to onset from injection	n=5 Within minutes (7), w/in 8 hrs (1)	n=5 Within minutes (4), w/in 24 hrs (1)
Recovery	Yes (0), No (6), Not reported (2)	Yes (0), No (7)
Concomitant local anesthetic injection	n=5 Yes (4), No (1) Bupivacaine (3), Lidocaine (2),	n=5 Yes (5), No (0) Bupivacaine (4), Lidocaine (1)
Outcome	Death (4), Hospitalization (5), Life threatening (2), Disability (2)	Death (1), Hospitalization (3), Life-threatening (1), Disability (2), Other (3)
Reporter	Physician (6), Pharmacist (1), Consumer (1)	Physician (3), Other healthcare professional (2), Attorney (2)
Report Type	Expedited (7), periodic (1)	Expedited (5), Direct (1), Periodic (1)
Year Received	1989, 1994, 1995, 1997, 1998, 1999, 2003, 2007	1996, 1997, 2004, 2005, 2008, 2009 (2)

^{iv} Intraarterial injections were reported as unintentional route of administration

Table 2. Characteristics of catastrophic neurologic events of AERS cases (U.S.) associated with betamethasone and dexamethasone as of 12/23/2009		
Parameter	Betamethasone N=4	Dexamethasone N=2
Gender	n=3 Male (1), Female (2)	Male (0), Female (2)
Age in years	n=3 Mean (60), Median (57) Range 42 to 80 yrs	n=1 22 yrs
Reported indication	n=3 Back pain/cervical pain (2), Radicular pain (1)	n=2 Back pain (2)
Dose	n=2 6 mg (2)	n=2 10 to 12 mg
Route of administration	Epidural injection (4)	Epidural (1), Unspecified injection (1)
Main event ^v	Quadraplegia (1), Paralysis (1), Myelitis transverse (1), Paresthesia (1)	Paraplegia (1), Artery embolus (1)
Estimated time to onset from injection	n=3 Within minutes (1), W/in 8 to 24 hrs (2)	Not given
Recovery	Yes (2), No (2) ^{vi}	Yes (1), No (0), Not reported (2)
Concomitant local anesthetics	n=3 Yes (2), No (1) lidocaine, marcaine	n=1 lidocaine (1)
Outcome ^{vii}	Hospitalization (2), Life threatening (1), Disability (1), Other (2)	Hospitalization (1), Life-threatening (1)
Reporter	Physician (2), Consumer (2)	Physician (2)
Report Type	Expedited (3), periodic (1)	Expedited (2)
Year Received	1995, 1998, 2006 (2)	1984, 1996

Refer to the summary of AERS cases for triamcinolone, betamethasone, dexamethasone in Tables 8, 9, and 10 respectively.

^v A case may have more than one reported outcome.

^{vi} Two cases reported partial recovery: continues to have bladder dysfunction (1), neurologic evaluation revealed sensory deficit (1)

^{vii} There may be more than one outcome per case.

Selected Cases

The two cases were selected to illustrate catastrophic events that occurred in the absence of concomitant local anesthetics or under a recommended procedural protocol such as fluoroscopic guidance.

METHYLPREDNISOLONE:

AERS ISR #622077 (received 1989)

A 27 year-old female patient initially received bupivacaine and lidocaine injections as stellate ganglion block^{viii} with no adverse effect. Four days later, these local anesthetics were co-administered with the methylprednisolone injection (route listed as unintentional intraarterial). The patient died within eight hours of the drug administration. A computerized axial tomography (CAT) scan revealed a lesion in the cerebellum and the consulting neurosurgeon suggested a brain stem infarct. The report cited the needle may have entered the vertebral artery during the procedure. No other significant details were noted.

AERS ISR #5186580 (Lit Report²², received 2006)

This report involved a 41- year-old male who experienced a fatal brainstem stroke following a cervical epidural steroid injection at the C-5-6 level. The injection was performed by an experienced anesthesiologist under fluoroscopic guidance. A test injection was performed with nonionic contrast prior to the steroid injection, confirming proper needle placement in the posterior epidural space. The patient received methylprednisolone 40 mg with preservative-free saline with no anesthetic. The patient developed nausea, vomiting, and headache within minutes of the procedure. He deteriorated clinically which was confirmed through repeated magnetic resonance imaging (MRI). The patient subsequently became unresponsive and died approximately seven days after methylprednisolone administration. The autopsy confirmed a brain stem infarction.

4.1.1 Summary of Case Series

From a sampling subset of 248 of the 1022 reports in AERS (as of December 23, 2009) citing neurologic-associated adverse events related to the products in question, we identified 21 unique domestic cases of catastrophic neurologic events occurring shortly after spinal injection.

The reported time to event onset after the injections was within minutes in over half of the cases for both particulate (12) and nonparticulate (1) preparations; in four cases, the events occurred within 24 hrs (particulate – 2, nonparticulate – 2), and in the remaining four cases the time to event onset was not reported.

^{viii} Stellate Ganglion Injection is an injection of local anesthetic in the "sympathetic nerve tissue."

The diagnoses of the events were confirmed through MRI and/or CT scan^{ix} in seven of the 21 cases (particulate – 4, nonparticulate – 3). The remaining 14 cases did not report MRI or CT scan results. The reported events after injection with particulate corticosteroids were: spinal cord infarction – 7, disability such as paraplegia – 3, stroke – 2, seizures – 2, nerve injury – 1, which include five fatal outcomes. The reported events after non-particulate steroid injection included quadraplegia – 3, possible nerve injury – 2, and artery embolus – 1. The patients did not recover from these reported adverse events in 68% of the cases (particulate – 13, nonparticulate – 2).

In summary, there were five deaths associated with the use of particulate steroids (nonparticulate - no deaths) where intravascular involvement was specifically mentioned in all five cases. The neurologic complications reported in these death cases were brain stem infarction – 3, grand mal convulsion – 1, brain edema/ seizure – 1.

4.2 LITERATURE

Eleven references reported 13 unique incidents of catastrophic neurologic AEs occurring during or within 48 hours of procedures; a 14th case is excluded for failure to identify the injected steroid. One or more catastrophic events were found for betamethasone, hydroxycortisone, methylprednisolone, and triamcinolone. No catastrophic events were found for dexamethasone. Age of affected individuals was 31 to 83 years, and the reported catastrophic events were more in men than women (see Table 3).

^{ix} One of the seven case (ISR #3288586) was confirmed through autopsy report: brain stem infarction

Table 3. Catastrophic Neurological Adverse Events Presenting during or within 24 hours Para-Vertebral Spinal Nerve injection^{3,4,5,6,7,8,9,10,11,12,13}

	N	Age (y)	Female (F) Male (M)	Procedure level	Outcome
ALL	13	59 (31 to 83)	F 3, M 10	--	
Non-Particulate	3	62 (39 to 83)	F 1, M 2	--	
Betamethasone	3	62 (39 to 83)	F 1, M 2	L3-4 (a) C5-6 (b) C5-6 (c)	Lower extremity paralysis, cord infarct (a); Seizure and hippocampal infarct on MRI (b); Posterior cord and cerebellar infarct (c)
Dexamethasone	0	-	-	-	
Particulate	10	58 (31 to 79)	F2 M8	--	
Hydrocortisone	1	65 y	M 1	L C5-6	Respiratory failure, tetraplegia, death 2 months later; Autopsy→ anterior cord infarct/disc embolus
Methylprednisolone	3	52 (31 to 79)	M 3	L3-4 (a) C7-T1 (b) C6-7 (c)	Lower extremity paralysis and lower spinal cord infarct (a); cerebellar infarct with herniation (b); temporary quadriparesis, MRI with unspecified ventral cord pathology negative for DJD
Triamcinolone	6	59 (48 to 71)	F2 M4	C6 (a) L2 (b) T11-12 (c) C5-6 (d) C1-2 (e) C5 (f)	Leg weakness, MRI with cord infarct C2-5 (a); sensory-motor impairment with spinal cord infarct by MRI (b); cord infarct T9 to conus with prolonged paresthesia/paraplegia (c); incomplete quadraparesis, neurosurgical procedure and death 1 day later; possible CBLR infarct (d); cerebral-CBLR-midbrain infarct and death (e); dysphasia, seizure, BLR and brain-stem infarct (f)

C=cervical, L=lumbar, T=Thoracic, DJD=degenerative joint disease, CBLR=cerebellar, MRI=magnetic resonance imaging

Literature further suggests that pathogenesis is related to two potential drug-related mechanisms and two traumatic mechanisms described below:

- Animal data suggesting that inadvertent intravascular injection of *particulate* steroids may cause neurologic injury via drug microemboli¹⁴

- Animal data supporting observations in humans that some steroids cause arachnoiditis when administered into spinal fluid^{15,16}
- Needle trauma precipitating disc emboli reported on autopsy¹⁷
- Needle trauma to the vertebral artery or the spinal cord¹⁸

5 DISCUSSION

Through the selection criteria outlined in the methods section of this document, we identified 21 cases¹⁹⁻²² in AERS and 13 cases^x in the literature citing various catastrophic neurologic adverse events after spinal injection of corticosteroid products. The reviewed data support the contention that serious neurologic complications may occur with the type of steroid injections covered by this review. Unintentional intravascular steroid placement is one potential causative mechanism.² The AERS data suggest that use of fluoroscopic imaging does not necessarily mitigate the risk of catastrophic outcomes. It is not possible to provide an estimated incidence for catastrophic neurologic outcomes with transforaminal steroid injection for various reasons including that corticosteroid injections are used for multiple indications and by multiple routes of administration, and the number of transforaminal steroid injection per year is also unknown. We note that fatal outcomes were reported in some AERS cases after administration of particulate rather than nonparticulate corticosteroid products. Reasons for this difference are unclear but are consistent with animal data¹⁴ which suggests that catastrophic neurologic outcome may be more likely with administration of particulate steroids than nonparticulate steroids, possibly due to micro-embolic phenomena with particulate steroid injection.

Of note is that transforaminal corticosteroid injection is a relatively common procedure and that the serious complications reviewed here are sequelae of off-label use. With only one exception, current product labeling do not allude to the risk related to use of these drugs as discussed in this review. As this use is off-label and as such use reflects otherwise accepted medical practice, it is problematic for FDA to use labeling revisions as a primary regulatory tool. Nonetheless, we believe it is important for FDA to communicate this potential risk to healthcare providers and patients.

6 CONCLUSION

Catastrophic neurologic adverse events including deaths after transforaminal epidural corticosteroid injections are reported in the AERS database and in the literature with use of both particulate and non-particulate products. The majority (81%) of the cases were temporally associated with the corticosteroid injections (i.e., there was a relatively short latency period between the injection and the adverse event). Additionally, the diagnoses of reported events were confirmed through MRI or CAT scans in a third of the cases. These findings support issuance of drug safety communication by FDA regarding the

^x AERS Case Series includes six literature reports, one of which is a duplicate report cited under the literature section (ISR# 6407456, triamcinolone case).

potential for neurologic complications, including permanent disability or death, with transforaminal epidural corticosteroid injections.

7 RECOMMENDATIONS

DPVII recommends a drug safety communication that warns of the potential for serious neurologic complications, including death or permanent disability, after transforaminal epidural corticosteroid injections.

APPENDICES

APPENDIX 1. CORTICOSTEROID PRODUCT INFORMATION

Table 4. Properties of Steroid Products²

Table 1									
Common Corticosteroid Injectables									
Steroid	Commercial Names	Equivalent Potency (mg)	Solubility*	Maximum Particle Size (µm) [†]	Particles >10 µm (%) [‡]	Particle Aggregation [†]	Benzyl Alcohol [†]	Polyethylene Glycol [†]	
Methylprednisolone acetate	Depo-Medrol, Solu-Medrol, Duralone, Medralone	4	0.001 [‡]	>500	45	Few	Yes	Yes	
Triamcinolone acetonide	Kenalog	4	0.0002 [‡]	>500	45	Extensive	Yes	No	
Betamethasone acetate,									
betamethasone sodium phosphate	Celestone Soluspan, Betaject	0.75	Acetate form, "practically insoluble"; sodium phosphate form, freely soluble	500	35	Some	No	No	
Dexamethasone sodium phosphate	Decadron Phosphate, Adrenocort, Decaject	0.75	Freely soluble	0.5	0	None	Yes	No	

* Information obtained from package inserts for each commercial product.

[†] References 23, 24. Maximum size of a red blood cell is approximately 10 µm.

[‡] Value is percent w/vol.

Table 5. Approved Corticosteroid Injectable Products (Reference Listed Drugs)

Drug	NDA	Applicant (s)	FDA Approval	Approved Route of Administration*				
				IA	IB	IL	IM	IV
Celestone Soluspan (betamethasone acetate; betamethasone sodium phosphate)	014-602	Schering	3/3/1965	X	X	X		
Dexamethasone	081-126, 087-440, 087-702	Teva, Luitpold, Baxter	8/31/1990 7/21/1982 7/7/1982	X		X	X	X
Kenalog-40 (Triamcinolone Acetonide)	014-901	Apothecon	2/1/1965,	X			X	
Depo-Medrol (methylprednisolone Acetate)	011-757	Pharmacia and Upjohn	5/27/1959	X		X	X	
Solu-Cortef (hydrocortisone sodium succinate)	009-866	Pharmacia and Upjohn	4/27/1955				X	X

*IA (intra-articular), IB (intrabursal), IL (intralesional), IM (intramuscular), IV (intravenous)

APENDIX 2. MEDRA SEARCH TERMS

Table 6. Selected PT list used for AERS search of steroid injections (N=107)	
Anaesthetic Complication	Incorrect Route Of Drug Administration
Neurological	
Arachnoiditis	Infarction
Areflexia	Ischaemic Cerebral Infarction
Arterial Haemorrhage	Ischaemic Stroke
Arterial Injury	Motor Dysfunction
Blindness	Nerve Injury
Blindness Cortical	Nerve Root Injury
Brain Death	Neurogenic Bladder
Brain Hypoxia	Neurogenic Shock
Brain Injury	Neurological Decompensation
Brain Oedema	Neurological Examination Abnormal
Brain Stem Infarction	Neurotoxicity
Brain Stem Ischaemia	Paraesthesia
Cerebellar Infarction	Paralysis
Cerebellar Ischaemia	Paralysis Flaccid
Cerebellar Syndrome	Paraparesis
Cerebral Artery Embolism	Paraplegia
Cerebral Artery Occlusion	Paresis
Cerebral Artery Thrombosis	Partial Seizures
Cerebral Disorder	Post Procedural Complication
Cerebral Haemorrhage	Post Procedural Haemorrhage
Cerebral Hypoperfusion	Pupillary Reflex Impaired
Cerebral Infarction	Quadriplegia
Cerebral Ischaemia	Respiratory Arrest
Cerebral Thrombosis	Respiratory Failure
Cerebral Venous Thrombosis	Retinal Vein Occlusion
Cerebrovascular Accident	Sensorimotor Disorder
Clonic convulsion	Sensory Disturbance
Clonus	Sensory Loss
Coma	Simple Partial Seizures
Complex Partial Seizures	Spastic Paralysis
Convulsion	Spinal Artery Embolism
Cranial Nerve Paralysis	Spinal Claudication
Deafness Neurosensory	Spinal Cord Disorder
Diaphragmatic Paralysis	Spinal cord infarction
Embolic Stroke	Spinal Cord Injury
Embolism	Spinal Cord Ischaemia
Embolism Venous	Spinal Cord Oedema
Encephalopathy	Spinal Cord Paralysis
Facial Paresis	Spinal Disorder
Faecal Incontinence	Spinal Shock
Grand Mal Convulsion	Sudden Death
Haemorrhage	Thalamic Infarction

Haemorrhagic Cerebral Infarction	Thrombosis
Hemiparesis	Urinary Incontinence
Hemiplegia	Vascular Injury
Hyperaesthesia	Vascular Occlusion
Hyperkinesia	Vasogenic Cerebral Oedema
Hyperreflexia	Vasospasm
Hypoaesthesia	Venous Thrombosis
Hypoaesthesia Facial	Vertebral Artery Thrombosis
Hyporeflexia	Visual Impairment
Iatrogenic Injury	Wrong Technique In Drug Usage Process
Incontinence	

APPENDIX 3. AERS DATA

Table 7. Selection of Individual AERS Cases					
Drug Name	Crude Count	Percent Sampled	Projected # of deaths from crude counts	Reasons for Exclusion	Final Number of Cases Included
Betameth	31	100% (31)	None	<p>N=27</p> <p>Non-Spinal Injections: Ankle/foot Inject (2), Topical Route (1), Intra-articular (1), Shoulder (1), Intra-dermal (1),</p> <p>Route not specified or Not a Neurological Catastrophic Outcome (18), Event prior to steroid injection (1),</p> <p>Insuff info to assess (2)</p>	4
Dexameth	310	20% (62)	None	<p>N=60</p> <p>Non-Spinal Injections: Chemo Therapy (40), Intravenous (7), Asthma Therapy (3), Intra-muscular (1), Oral (2), Axillary nerve block (1)</p> <p>Route Not Specified or Not a Neurological Catastrophic Event (4), Duplicates (2)</p>	2
Hydrocort	97	30% (29)	None	<p>N=29</p> <p>Non-Spinal Injections: Chemo Therapy (20), Asthma Therapy (2), Rectal Route (1)</p>	

				Route not specified or Not a Neurological Catastrophic Event (6)	
Methylpred	491	20% (98)	19 (4%, 9/491)	<p>N=90</p> <p>Route Not Specified or Not a Neurological Catastrophic Event (29), Intravenous (14), Intra-theal (6), Recovery^{xi} w/in 24 hrs (5), Subarachnoid space (2)</p> <p>Non-Spinal Injections: Chemo Therapy (11), Asthma Therapy (7), Inject into eye, hand, heel, knee, shoulder (6), Oral (3)</p> <p>Insuff Info to Assess (4), Duplicates (3),</p>	8
Triamcin	93	30% (28)	4 (4%, 4/93)	<p>N=21</p> <p>Non-Spinal Injections: Intra-articular (4), Intravitreal (3), Hip inject (1), Asthma Therapy (1)</p> <p>Route Not Specified or Not a Neurological Catastrophic Outcome (7), Intrathecal (2), Event occurred 24 hrs post triamcin injection (1), Unlikely related to triamcin injection (1)</p> <p>Insuff info to assess (1)</p>	7
TOTAL	1022	248	23	91	21

Betameth (betamethasone), Dexameth (dexamethasone), Hydrocort (hydrocortisone), Methylpred (methylprednisolone)

^{xi} Any event

Table 8. AERS Cases of Catastrophic Events Associated with Triamcinolone Spinal Injections (N=7)						
ISR#	Age (yrs) Sex	Adverse Event Reporter	Estimated time to event onset after injection	Out-come	Concom injections Indication	Summary of clinical notes
6407456 (LIT)	48 F	Cerebellar Infarction Pharm	Immed	DE	Bupivacaine, midazolam, fentanyl Intervertebral disc protrusion (auto injury)	Pt received C5-C6 transforaminal epidural injection under fluoroscopic guidance. Pathology revealed bilateral cerebellar infarction as well as left occipital cortex infarction. Consistent with vertebral artery injectin or terminal branch injury or occlusion.
4701577	53 M	Quadriplegia, spinal cord infarction MD	15 min	OT	Bupivacaine Cervical pain, multilevel degenerative disc disease	C6 transforaminal injection under fluoroscopic guidance given. Developed weakness in left arm and bilateral lower limbs. Consistent with diffuse vascular infarct to cervical cord, resulting in motor-incomplete tetraplegia. No direct trauma to cord.
6463890 (LIT)	55 F	Paraplegia, spinal cord ischaemia HCP	Within a minute	DS	Bupivacaine Disc herniation at L1-2	Initial placement of needle showed back bleeding on removal of stylet which resolved after needle was repositioned during a transforaminal epidural steroid injection. CT showed no evidence of epidural hematoma. Spinal cord ischaemia diagnosed on clinical and radiological findings. Pt remains paraplegic.
5946840	56 F	Para-thesias, neuro-pathy Attorney	Not reported	OT	Not reported Disc annular tear	Pt developed extreme parathesias and burning neuropathy after receiving two epidural injections one month apart. Additional symptoms included muscle pain, weakness, twitching in eyes, thumbs, nausea, panic attacks, insomnia, skin eruptions. Pt did not recover at time of report.
4493127	71 M	Paralysis, vision impaired Consumer	w/in 24 hrs	HO	Not reported Back pain	Pt received Kenalog 40 mg injection (route not specified) and developed mild paralysis and numbness (details not given). Pt was told he had nerve damage. Med hx included open heart surgery, two bypass surgeries, CHF. No further details given.
1915477	74 F	Quadriplegia, cardiac arrest	w/in minutes	LT, HO, DS	Marcaine Neck pain,	Pt was found slumped in her chair within minutes after epidural injections of Aristocort and Marcaine. Respiratory and cardiac arrest was suspected per reporter.

		MD			cervical spondylosis	The pt eventually regained some orientation but remains quadriplegic. Reporting physician suspects permanent disability. No further details or medical hx were given.
1795939	unk unk	Spinal paralysis from T-11 down	Immediate	HO	Lidocaine Pain	Pt experienced spinal paralysis from T-11 down immediately after receiving spinal injection of lidocaine mixed with Aristocort. Med hx included laminectomy ~10 yrs prior to procedure and S/P auto vehicle accident. Cause of the paralysis was not determined at time of report. No further details.

Table 9. AERS Cases of Catastrophic Events Associated with Betamethasone Spinal Injections (N=4)						
ISR#	Age (yrs) Sex	Adverse Event Reporter	Estimated time to event onset after injection	Outcome	Concom injections Indication	Summary
5194750	80 F	Flaccid Paralysis HP	w/in 24 hrs	HO	Lidocaine, Not reported	Pt could not move her lower extremities after receiving a nerve block via epidural injection with celestone soluspan. She was treated with dexamethasone IV, Lortab, and Heparin while hospitalized for six days. The events resolved without sequelae. No medical hx or further details given.
1638328	57 M	Quadri-plegia MD	w/in minutes	HO, LT, DS	Omniquest (contrast agent)	Pt received a series of celestone soluspan epidural injections for cervical pain sustained from an auto accident. A 4 th injection was given with CT guidance and the pt immediately developed laryngospasm. Thirty-minutes later he went into respiratory arrest (intubated). CT Scan did not show any penetration of the spinal cord during the procedure. Upon awaking in the ICU, complete quadriplegia was noted without cranial or cognitive impairment. Also, had neurogenic bowel and bladder requiring use of a catheter. Pt had a hx of cervical laminectomies ~20 yrs prior to this procedure. A year later, pt has improved with physical and occupational therapy. Continues to have bladder dysfunction.
3168014	NR NR	Paresthesia MD	NR	OT	NR Unk	Epidural injection of celestone soluspan was given under fluoroscopy with dye. MRI showed no changes. A neurological evaluation revealed sensory deficit. No further details.
4946477	42	Myelitis	w/in 8 hrs	OT	Bupiva-	A pt with an undiagnosed Bechet's Disease

(Lit)	F	transverse MD			caine Radicular pain	received a CT guided nerve root injection to treat pain (at L2). Within 8 hrs of injections w/ betamethasone phosphate and bupivacaine, the pt felt bilateral lower extremity weakness, urinary urgency and paresthesias extending to T12. Vascular cause was less likely based on the timing of the event. Complete motor recovery was reported w/ no evidence of intraparenchymal bld in the needle, so direct spinal cord trauma was ruled out per report .
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Table 10. AERS Cases of Catastrophic Events Associated with Dexamethasone Spinal Injections (N=2)						
ISR#	Age (yrs) Sex	Adverse Event Reporter	Estimated time to event onset after injection	Outcome	Concom injections Indication	Summary
320904	NR F	Paraplegia MD	NR	RI	Methylpred, lidocaine Back pain	Pt experienced paraplegia after injection w/ epidural dexameth, methylpred, and lidocaine. Pt was slowly recovering at time of report. No further details given.
1729909	NR F	Artery Embolus MD	NR	LT	Dexameth NR	While on therapy with dexamethasone injection, pt developed superior mesenteric artery embolus. Pt lost most of her bowel as a result. No further details given.

NR (not reported); Concom (concomitant); Methylpred (methylprednisolone), Dexameth (dexamethasone)

Table 11. AERS ISR Numbers							
Betameth		Dexameth		Methyl		Triamcin	
ISRNUM	MFCNTRL	ISRNUM	MFCNTRL	ISRNUM	MFCNTRL	ISRNUM	MFCNTRL
1638328	95060086	320904	22790	622077	186211757	6407456	14391320
3168014	97-10-0158	1729909	WAES96021815	5186580	150628USA	4701577	2005AC00903
4946477	2006-03-0141			1608973	277811757	5946840	CTU 355374
5194750	2006UW28205			1994376	335211757	6463890	2009SE29022
				3288586	3483/11757	1915477	897050001S
				1523055	277711757	4493127	12743100
				4144187	2003163803US	1795939	500065501
				5555955	2007101421		

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
SAFETY-822	ORIG-1	FOOD AND DRUG ADMINISTRATION	CORTICOSTEROIDS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOANN H LEE

05/17/2010

Ethan,
Per your request, I've revised your section.

ETHAN D HAUSMAN

05/17/2010

AFROUZ R NAYERNAMA

05/17/2010

ROBERT M BOUCHER

05/18/2010

<p align="center">Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology</p>	
Date:	February 23, 2010
Application Type/Number:	NDA 011757 (Pharmacia and Upjohn) NDA 014602 (Schering) NDA 014901 (Apothecon) ANDA 081126 (Teva Parenteral), 087440 (Luipold), and 087702 (Baxter Healthcare)
To:	Badrul Chowdhury, MD, Director Division of Pulmonary, Allergy and Rheumatology (DPARP)
Through:	Carlos M Mena-Grillasca, RPh, Team Leader Kellie Taylor, PharmD, MPA, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Chi-Ming Tu, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Catastrophic Neurologic Outcome after Transforaminal Epidural Steroid Injection
Drug Name(s):	Steroid Injections, Reference Listed Drugs: Celestone Soluspan (betamethasone acetate; betamethasone sodium phosphate) NDA 014602 Dexamethasone sodium phosphate ANDA 081126, 087440, 087702 Depo-Medrol (methylprednisolone acetate) NDA 011757 Kenalog-40 (triamcinolone acetonide) NDA 014901
Applicant/sponsor:	Apothecon, Baxter Healthcare, Luipold, Pharmacia and Upjohn, Teva Parenteral, Schering
OSE RCM #:	2009-2228

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EXECUTIVE SUMMARY

This review evaluates the 21 unique domestic cases of catastrophic neurologic events occurring shortly after spinal injections of corticosteroids identified by the Division of Pharmacovigilance II in their review dated May 14, 2010 (OSE RCM# 2009-2228). The Division of Pulmonary, Allergy and Rheumatology Products requested DMEPA to determine if these catastrophic neurologic events are results of medication errors; and if so, to provide recommendations to prevent such medication errors.

Transforaminal epidural injection of corticosteroids is an off-label use. Although off-label use is generally not considered a medication error, six of the twenty-one cases were considered to be definitively associated with a wrong route of administration (i.e. inadvertent intra-arterial). The remaining cases either did not describe a medication error (n=2) or did not provide enough information to determine whether a wrong route of administration error occurred or not (n=13). The medication error cases all involved methylprednisolone, but the catastrophic neurologic outcomes occurred with three other corticosteroids as well. Because the targeted space in an epidural injection is so small and blood vessels may be punctured during the procedure, it is not clear if the root cause of the medication error is due to the use of corticosteroids via epidural injection or the technique itself. Based on the information available, we cannot conclude that wrong route of administration errors contribute to the catastrophic neurologic event after spinal injection of corticosteroids because the catastrophic neurologic outcomes have been reported when epidural corticosteroid injections are administered as intended and when administered via the wrong route. For this reason, we concur with DPV II's recommendation for a drug safety communication that warns of the potential for serious neurologic complications after transforaminal epidural corticosteroid injections.

Although unrelated to the epidural injection, we also identified one medication error case that described an intrathecal injection of Depo-Medrol which resulted in paraplegia. Currently, only Depo-Medrol has a labeled contraindication for intrathecal administration, while other products such as Celestone Soluspan and Kenalog-40 have labeled warning statements. Therefore, further discussion within the Center may be warranted regarding the need to include a similar intrathecal contraindication for other injectable corticosteroids (i.e. betamethasone, dexamethasone, and triamcinolone).

1 INTRODUCTION

This review responds to a consult from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to evaluate the 21 cases identified by the Division of Pharmacovigilance II (DPV II) in relation to the transforaminal epidural use of corticosteroids (OSE RCM# 2009-2228, dated May 14, 2010). The focus of this review is to determine if these reported catastrophic neurologic events are resulted from medication errors; and if so, to provide recommendations to prevent such medication errors.

2 BACKGROUND

In November 2009, the Division of Analgesia, Anesthesia, and Rheumatology Products (DAARP) received a correspondence from an anesthesiologist at Harvard University.

The anesthesiologist raised a concern regarding depot formulations of steroids being used commonly off-label for spinal injections to treat pain, but were inadvertently injected intra-arterially which results in catastrophic neurologic injuries. A Tracked Safety Issue (TSI# 822) for corticosteroids and catastrophic neurologic events with epidural injection was opened on November 11, 2009.

DPV II performed a search of the Adverse Event Reporting System (AERS) and the literature for catastrophic neurologic events associated with transforaminal epidural steroid injections used for the treatment of back pain to determine if a safety communication is needed. Uses other than back pain (e.g. chemotherapy) were excluded from DPV II's search. After reviewing the AERS database, DPV II found that catastrophic neurologic outcomes were reported after transforaminal epidural steroid injections. Outcomes reported were spinal cord infarction, paraplegia, quadriplegia, cortical blindness, stroke (including brainstem), and death (OSE RCM# 2009-2228, dated May 14, 2010).

DPV II's literature search findings suggest the pathogenesis is related to several possible mechanisms:

- Animal data suggesting that inadvertent intravascular injection of particulate steroids may cause neurologic injury via drug microemboli
- Animal data supporting observations in humans that some steroids cause arachnoiditis when administered into spinal fluid
- Needle trauma precipitating disc emboli reported on autopsy
- Needle trauma to the vertebral artery or the spinal cord

A Safety Issues Team (SIT) meeting was held on June 30, 2010 to discuss DPV II's findings and the recommendation for a drug safety communication. After multiple meetings from June to December 2010, the SIT decided that it is best to bring this issue to the attention of senior management because the complexity of the issues at hand. The SIT agreed to present the findings at the Center Director's Briefing scheduled for March 7, 2011.

3 REGULATORY HISTORY

A literature review indicates that transforaminal epidural steroid injections have been used for the treatment of back pain in clinical practice since at least 1961. However, no steroid preparation has an approved usage for transforaminal epidural injection.

The Adverse Reactions section of the approved label for Depo-Medrol (methylprednisolone; NDA 011757) lists arachnoiditis, bowel/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizures, sensory disturbances as adverse reactions that have been reported with the intrathecal and epidural route of administration. Also, Depo-Medrol sterile aqueous suspension is specifically contraindicated for intrathecal administration based on reports of severe medical events such as arachnoiditis following such administration.

The approved labels for Celestone Soluspan (betamethasone; NDA 014602), dexamethasone (ANDA 081126, 087440, 087702) and Kenalog-40 (triamcinolone acetate; NDA 014901) are silent on epidural route of administration. Additionally, Celestone Soluspan and Kenalog-40 have Warning Statements for intrathecal administration based on neurologic reports of severe medical events (gastrointestinal, neurologic and psychiatric adverse reactions) associated with intrathecal administration (See Appendix 9.1 for reference listed drug products).

4 METHODS AND MATERIALS

DMEPA reviewed the case narratives of the 21 cases previously identified from the AERS database search performed by DPV II (OSE RCM# 2009-2228, dated May 14, 2010). We evaluated these cases to determine if a medication error occurred during the spinal injection of corticosteroids (See Appendix 9.2 for summary of case narratives and Appendix 9.3 for a listing of ISR#).

5 RESULTS

Products involved in these 21 cases included methylprednisolone (n=8), triamcinolone (n=7), betamethasone (n=4), and dexamethasone (n=2). One case (ISR# 320904) involved the use of both dexamethasone and methylprednisolone. In line with DPV II's Review, this case has been listed under dexamethasone for analysis purposes.

Patient demographics included both male (n=6) and female (n=12), and the median age was 55 years old (range 27 to 80). Twelve of the 21 cases reported an indication for the treatment of various types of pain, ranging from neck pain to post herpetic neuralgia. Six of the 21 cases reported the dosage of the drug product: triamcinolone (n=3; dosage range from 40 to 80 mg), betamethasone (n=2; dosages were 6 mg and 18 mg) and methylprednisolone (n=1; dosage was 120 mg). After reviewing the approved label for these corticosteroids, the reported dosages fell within the usual dosages for the products and did not present an overdose¹. However, since this procedure is off-label, it is unclear if the reported doses would be appropriate for this route of administration or if a lower dose would be required.

Of the 21 AERS cases, six (n=6) cases were identified as medication errors associated with wrong route of administration, two (n=2) cases confirmed absence of medication error, and 13 cases where we could not determine whether a medication error occurred due to lack of reported details. The following subsections provide further analysis of our evaluation of 21 cases.

5.1 WRONG ROUTE OF ADMINISTRATION (N=6)

Five (n=5) cases involved inadvertent intra-arterial injections of Methylprednisolone and one (n=1) case involved an intrathecal injection of Methylprednisolone. Although the

¹Labeled dosages for approved indications: triamcinolone labeled range from 2.5 mg to 100 mg, betamethasone from 0.25 mg to 9 mg and daily doses of 30 mg for treatment of acute exacerbation of multiple sclerosis, and methylprednisolone from 4 to 120 mg.

intended route of administration was not always reported in the five cases, these were classified as wrong route errors because the case narratives stated an “inadvertent” route of administration.

All 6 cases involved Methylprednisolone injection. None of cases reported the use of fluoroscopic or CT guidance during the procedure.

In the case that reported an intrathecal administration, the case narrative did not indicate if the physician was performing an off-label injection under the knowledge of the labeled contraindication for intrathecal administration or if the physician was not aware of the contraindication. Therefore, this case is considered a medication error. Table 1 below summarizes these cases.

Table 1. Medication Errors Associated with Wrong Route of Administration

Drug	ISR#	Intended Route	Administered Route	Imaging guidance	Indication	Outcome
Methylprednisolone	3288586	NR	intra-arterial	NR	Post herpetic neuralgia	Death
Methylprednisolone	1994376	NR	intra-arterial	NR	NR	Death
Methylprednisolone	622077	NR	intra-arterial	NR	Stellate ganglion block	Death
Methylprednisolone	1523055	Epidural	intra-arterial	NR	NR	stroke
Methylprednisolone	4144187	NR	intra-arterial	NR	NR	Stroke
Methylprednisolone	1608973	IT	NR	NR	NR	paraplegia

IT: Intrathecal; NR: Not reported.

5.2 NO MEDICATION ERROR (N=2)

Two cases described transforaminal epidural Triamcinolone injection under fluoroscopic guidance where adequate needle tip placement was confirmed. Since the intended route of administration was confirmed, these cases were eliminated as an error. The outcomes reported were death and paraplegia.

Despite the use of fluoroscopy to confirm needle tip placement in these cases, catastrophic neurologic outcomes still occurred. Table 2 below summarizes the two cases.

Table 2. Cases without Medication Error

Drug	ISR#	Intended Route	Administered Route	Imaging guidance	Indication	Outcome
Triamcinolone	6407456	Epidural	epidural	Fluoroscopy	Pain from herniated nucleus pulposus	Death
Triamcinolone	6463890	Epidural	epidural	Fluoroscopy	Acute on chronic disk herniation at L1-2	Paraplegia

5.3 CASES WHERE MEDICATION ERRORS CANNOT BE DETERMINED (N=13)

There were 13 cases where only the intended route of administration was reported. Since there is no information in the case narrative to suggest that the injection was not performed as intended, a determination could not be made with regard to whether a medication error occurred or did not occur.

Of these 13 cases, three (n=3) cases were performed under fluoroscopy and two (n=2) under CT guidance. The intended route of administration was epidural in these five cases. However, since the narrative did not confirm needle placement, it is unknown whether the drug product was actually injected into the epidural space or administered in an unintended area. Regardless, in these cases catastrophic neurologic outcomes still occurred. The associated outcomes reported for these cases were quadriplegia (n=2), paraplegia (n=1), paraparesis (n=1) and motor weakness (n=1).

The remaining eight cases (n=8) did not report the use of imaging guidance during the procedure, the associated outcomes reported were paralysis (n=2), death (n=1), quadriplegia (n=1), paraplegia (n=1), paraparesis (n=1), parathesia (n=1) and arterial embolus (n=1). Table 3 below describes these 13 cases.

Table 3. Cases Lacking Detail for Determining Occurrence of Medication Error

Drug	ISR#	Intended Route	Administered Route	Imaging guidance	Indication	Outcome
Betamethasone	3168014	Epidural	NR	Fluoroscopy	NR	Motor weakness
Betamethasone	4946477	Epidural	NR	CT	L2 radicular pain	Paraparesis
Betamethasone	5194750	Epidural	NR	NR	NR	Paraparesis
Betamethasone	1638328	Epidural	NR	CT	Neck pain	Paraplegia
Dexamethasone	1729909	NR	NR	NR	NR	Arterial embolus
Dexamethasone	320904	Epidural	NR	NR	NR	paraplegia
Methylprednisolone	5186580	Epidural	NR	NR	NR	Death
Methylprednisolone	5555955	Epidural	NR	Fluoroscopy	Pain of anterior spinal artery syndrome	Quadriplegia
Triamcinolone	4493127	Spinal	NR	NR	Lower back pain	Paralysis
Triamcinolone	1795939	Spinal	NR	NR	Pain	Paralysis
Triamcinolone	5946840	Epidural	NR	NR	Torn disc	Parathesia
Triamcinolone	4701577	Epidural	NR	Fluoroscopy	Chronic cervical pain	Quadriplegia
Triamcinolone	1915477	Epidural	NR	NR	Neck pain	Quadriplegia

NR: Not reported.

6 DISCUSSION

Only six of the 21 cases evaluated could definitively be described as a medication error involving a wrong route of administration (i.e. inadvertent intra-arterial). Since the catastrophic neurologic outcomes occurred with or without medication errors, it does not appear that the medication error itself contributes to the catastrophic neurologic adverse events.

For the cases involving a medication error, we could not determine if the root cause for the medication error is the use of this class of products via epidural injection or the technique itself. The epidural injection itself presents an inherent risk because the procedure requires extreme precision to deliver the drug into such a small and narrow epidural space. During this procedure, the risk of puncturing a blood vessel is increased due to the anatomical limitations. In addition, the transforaminal epidural injection procedure also has an inherent risk of needle trauma, which may also precipitate an

embolus and potentially cause the same catastrophic neurological adverse events as a drug microembolus.

Although not relevant to the evaluation of epidural injections, our review noted that one of the six medication error cases involving an intrathecal injection of Depo-Medrol. Currently, Depo-Medrol is the only corticosteroid with a labeled contraindication for intrathecal route of administration. Other products such as Celestone Soluspan and Kenalog-40 have labeled warning statements for intrathecal administration. We question the need for including similar contraindications in other injectable corticosteroids.

7 CONCLUSION AND RECOMMENDATION

Despite the lack of a clear association between the wrong route of administration and catastrophic neurologic outcome, two cases provide some evidence that these outcomes can occur when epidural injections of corticosteroid were performed as intended. For that reason, we concur with DPV II's recommendation for a drug safety communication that warns of the potential for serious neurologic complications after transforaminal epidural corticosteroid injections.

Additionally, our review noted inconsistency across the labeling of corticosteroids. We note that further discussion within the Center may be warranted regarding the need to include similar intrathecal contraindication for other injectable corticosteroids (i.e. betamethasone, dexamethasone, and triamcinolone).

If you have further questions or need clarifications, please contact Sean Bradley, OSE project manager, at 301-796-1332.

8 REFERENCES

8.1 REVIEWS

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5. OSE Review # 2009-2228, Catastrophic Neurologic Outcome after Transforaminal Epidural Steroid Injection, Lee JH. May 14, 2010.

8.2 DATABASES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

9 APPENDIX

9.1 APPROVED PRODUCTS (REFERENCE LISTED DRUGS)¹

Drug Product	NDA	Applicant(s)	FDA Approval Date	Approved Route of Administration ²				
				IA	IB	IL	IM	IV
Celestone Soluspan (betamethasone acetate; betamethasone sodium phosphate)	014602	Schering	3/3/1965	x	x	x	x	
Dexamethasone	081126 087440 087702	Teva, Luitpold, Baxter	8/31/1990 7/21/1982 7/7/1982	x		x	x	x
Kenalog-40 (Triamcinolone Acetonide)	014901	Apothecon	2/1/1965	x			x	
Depo-Medrol (methylprednisolone Acetate)	011757	Pharmacia and Upjohn	5/27/1959	x		x	x	

¹Table adapted from DPV II review, OSE RCM# 2009-2228, dated May 14, 2010.

²IA: intra-articular; IB: intrabursal, IL: intralesional, IM: intramuscular, IV: intravenous

9.2 AERS CASE SUMMARY NARRATIVE (N=21)

Categorization	Drug	ISR#	Intended Route	Administered Route	Imaging guidance	Indication	Outcome	Summary of Case Narrative
Medication Error	Methylprednisolone	3288586	NR	intra-arterial	NR	Post herpetic neuralgia	Death	65 yo M pt received Depo-Medrol and an unspecified local anesthetic (either lidocaine or marcaine) for post herpetic neuralgia. Following inadvertent intra-arterial inj in the neck area, within a few seconds the pt became unresponsive and required resuscitation. Pt was transferred to ICU and declared brain dead within one to two days. Autopsy result not available. Reporting physician believed the autopsy indicated the drugs were injected into the vertebral artery causing brain stem infarct.
Medication Error	Methylprednisolone	1994376	NR	intra-arterial	NR	NR	Death	40 yo F pt erroneously received an intravenous administration of Depo-Medrol and subsequently died. Cause of death unknown. Additional information added injection of Depo-Medrol was inadvertently injected into a neck artery which leads directly to the brain. Pt immediately had seizure and developed respiratory distress, placed on ventilator and admitted to ICU. Pt subsequently died of respiratory arrest the following day.
Medication Error	Methylprednisolone	622077	NR	intra-arterial	NR	Stellate ganglion block	Death	27 yo F pt received Depo-Medrol, Marcaine and Xylocaine on (b) (6) for stellate ganglion block following MVA. Pt experienced possible brain stem infarct. CAT scan revealed lesion in cerebellum. Possibility that needle entered the vertebral artery; pt died six to eight hr following inj. 4 days prior to this inj, pt received only marcaine and xylocaine with no adverse effects.
Medication Error	Methylprednisolone	1608973	IT	NR	NR	NR	paraplegia	45 yo M pt received Depo-Medrol 40 mg/mL 3 mL containing benzyl alcohol and lidocaine 2 mL via intrathecal injection. Pt experienced paraplegia. MRI revealed abnormality of conus medullaris. No further details at time of report.
Medication Error	Methylprednisolone	1523055	Epidural	intra-arterial	NR	NR	stroke	F pt received Depo-Medrol inj to trigger point in occipital area in (b) (6). Pt immediately experienced a stroke. There was speculation that needle may have penetrated the patient's vertebral artery. Pt hospitalized. No further details.
Medication Error	Methylprednisolone	4144187	NR	intra-arterial	NR	NR	Stroke	Pt received Depo-Medrol sterile aqueous suspension intra-arterially and experienced a stroke. No further details.
No Medication Error	Triamcinolone	6407456	Epidural	epidural	Fluoroscopy	Pain from herniated nucleus pulposus	Death	48 yo F pt received Triamcinolone acetate, bupivacaine HCl, midazolam 2 mg and fentanyl 100 mcg via C5-C6 transforaminal epidural inj under fluoroscopic guidance. Hx notable for MRI evidence of C5-C6 herniated nucleus pulposus. Under direct fluoroscopic visualization, adequate needle tip position in lateral mass was shown under image intensifier. Bupivacaine 0.25% 2 mL mixed with Triamcinolone 80 mg was inj, total fluoroscopy time was 7 seconds, pt conscious throughout procedure. Upon self-transfer from C-arm table to stretcher, pt became unresponsive. Approximately 1 hr later, pt

Categorization	Drug	ISR#	Intended Route	Administered Route	Imaging guidance	Indication	Outcome	Summary of Case Narrative
								regained consciousness, found complete loss of movement in right arm and weakness in left grip. Pt expired the following day. Pathology revealed bilateral cerebellar infarction and left occipital cortex infarction.
No Medication Error	Triamcinolone	6463890	Epidural	epidural	Fluoroscopy	Acute on chronic disk herniation at L1-2	Paraplegia	55 yo F pt received Triamcinolone (Kenalog) 1 mL and 0.25% Bupivacaine via transforaminal epidural inj. Initial needle placement showed back bleeding on removal of stylet, needle repositioned and needle tip was reportedly confirmed following inj of 2 mL myelographic contrast. Within min of inj, pt developed bilateral lower extremity weakness, progressed to flaccid paralysis. CT of thoracolumbar spine within 1.5 hr demonstrated no evidence of epidural hematoma. MRI of spine 4 hr after inj demonstrated subtly increased signal intensity within central gray matter of distal thoracic cord with restricted water diffusion in same area. Catheter-directed spinal angiography performed, showed abnormality. Thoracolumbar spinal angiogram failed to demonstrate origin of artery of Adamkiewicz. Acute spinal cord ischemia diagnosed on clinical and radiologic findings. Pt remained paraplegic at time of report.
Undetermined	Betamethasone	3168014	Epidural	NR	Fluoroscopy	NR	Motor weakness	Pt received Celestone Soluspan epidural inj on 10/00/1997. Pain, tingling in legs and a "funny sensation" with mild motor weakness on left side noted. Inj performed under fluoroscopy with dye. MRI showed no changes. Neurological evaluation revealed sensory deficit.
Undetermined	Betamethasone	4946477	Epidural	NR	CT	L2 radicular pain	Paraparesis	42 yo F pt with undiagnosed Behcet's Dz received CT guided nerve root inj to alleviate L2 radicular pain. She had noted frequent development of pustules and swelling at the site of venipuncture, consistent with a pathergy response. A 22 gauge needle was placed adjacent to L2 nerve root and Marcaine 0.5% 1 mL and Celestone 6 mg was injected. Within 8 hrs, pt experienced bilateral lower extremity weakness, urinary urgency, paresthesias. MRI the following day revealed edematous changes from conus medullaris to T9. Brain and cervical spine MRI normal. Pt made significant, albeit incomplete recovery. "Neurologic symptoms did not begin until many hours after the procedure making a vascular cause less likely." Pt had complete motor recovery with no evidence of intraparenchymal blood so direct needle trauma to spinal cord was unlikely. Literature author suggested transverse myelitis in this pt was related to Behcet's Dz and a pathergy response in the spinal cord.
Undetermined	Betamethasone	5194750	Epidural	NR	NR	NR	Paraparesis	80 yo F received lidocaine 1% 2 mL for nerve block, Celestone Soluspan suspension 18 mg via epidural inj and lorazepam 1 mg PO on (b) (6). Pt experienced inability to move lower extremities, flaccid paraparesis of lower extremities and numbness of legs and hypoesthesia extending to groin

Categorization	Drug	ISR#	Intended Route	Administered Route	Imaging guidance	Indication	Outcome	Summary of Case Narrative
								and the perianal skin. Pt hospitalized (b) (6), tx with Decadron IV, Lortab, Heparin. Events resolved at time of report.
Undetermined	Betamethasone	1638328	Epidural	NR	CT	Neck pain	Paraplegia	57 yo M pt received a series of Celestone Soluspan Inj. First 2 inj unremarkable. 3rd Inj in Aug 1994, laryngeal spasm and hoarseness noted. Pt returned to normal after 6 hrs. 4th CT assisted inj on (b) (6), laryngospasm with edema and hypoxemia noted. 30 min later, pt experienced respiratory arrest. CT scan showed no penetration of spinal cord during procedure. Pt intubated, transferred to ER. MD reported event clinically resembled anaphylactic rxn. Pt remembered having neck pain and receiving inj, but did not remember anything until woke up in ICU. Upon awakening, complete quadriplegia noted without cranial or cognitive impairment. Pt had neurogenic bowel & bladder required use of catheter. Tracheostomy performed in (b) (6), and 2nd tracheostomy was performed date unknown. Pt then experienced UTI, respiratory inf. stress ulcer, anemia, and malnutrition. Transferred to another hospital (b) (6) for in-pt spinal cord injury rehabilitation. In 1995, pt ambulation improved with rehabilitation but remains on condom catheter, slight improvement in upper extremities.
Undetermined	Dexamethasone	1729909	NR	NR	NR	NR	Arterial embolus	F pt on tx of Dexamethasone injection. While on tx, pt developed a superior mesenteric artery embolus. At time of report, pt lost most of her bowel as a result. No further details were provided.
Undetermined	Dexamethasone	320904	Epidural	NR	NR	NR	paraplegia	F pt received Depo-Medrol, Decadron and Xylocaine via epidural inj on 8/9/1984. Pt developed paraplegia. Pt is slowly recovering from paraplegia with physical therapy and psychiatric support at time of report.
Undetermined	Methylprednisolone	5186580	Epidural	NR	NR	NR	Death	41 yo M pt received a series of Methylprednisolone via cervical epidural inj. Upon 3rd inj of Methylprednisolone acetate 40 mg and saline, within minutes, pt developed headache, N/V. 2 hr later, pt showed improvement and discharged. Approximately 7.5 hr after procedure, pt called for help, pt experienced progressive weakness in all extremities and slurred speech. Level of consciousness deteriorated within 30 min. Pt taken to ER and intubated. Pt became unresponsive, nonreactive pupils. MRI revealed diffuse ischemic infarction. Pt was comatose and repeat MRI and magnetic resonance angiography revealed progression of ischemia. Pt received Methylprednisolone IV x 5 days due to possibility of inflammatory process, but no improvement. Pt continued to deteriorate and died. Autopsy showed hemorrhage and edema in brainstem.
Undetermined	Methylprednisolone	5555955	Epidural	NR	Fluorosc	Pain of anterior	Quadriplegia	66 yo F pt received Depo-Medrol via cervical epidural inj under fluoroscopy for relief of intractable pain developed post procedure anterior spinal artery

Categorization	Drug	ISR#	Intended Route	Administered Route	Imaging guidance	Indication	Outcome	Summary of Case Narrative
						spinal artery syndrome		syndrome. Within 45 min, pt developed acute onset flaccid quadriplegia. Day 2 post-procedure, MRI showed edema of entire C-spine and restricted diffusion at C4-6 confirming likelihood of cord infarct. At 3 weeks, pt remained quadriplegic. Literature author concludes posterior placement of the needle in transforaminal inj is not necessarily safe despite avoiding vertebral artery.
Undetermined	Triamcinolone	4493127	Spinal	NR	NR	Lower back pain	Paralysis	71 yo M pt received Triamcinolone 40 mg via inj into lower spine for tx of lower back pain on (b) (6). On same day, pt passed out and experienced hypotension, mild paralysis, numbness, visual impairment and optic nerve damage. Pt remained in-pt for couple more weeks before transfer to rehabilitation.
Undetermined	Triamcinolone	1795939	Spinal	NR	NR	Pain	Paralysis	Pt received caudal anesthetic, lidocaine mixed with Aristocort via spinal inj on 1/22/1995. Pt experienced immediate spinal paralysis from T-11 down. No intervention as of 1/25/95. No cause determined by doctor. S/P MVA, early (b) (6) with radiating pain down his leg. No further details.
Undetermined	Triamcinolone	5946840	Epidural	NR	NR	Torn disc	Parathesia	56 yo F pt received two Kenalog (Triamcinolone) epidural inj for torn disc on 7/10/2008. Pt experienced extreme parathesia in lower extremities, then a few weeks later in upper extremities.
Undetermined	Triamcinolone	4701577	Epidural	NR	Fluorosc opy	Chronic cervical pain	Quadriplegia	53 yo M pt received 0.75% bupivacaine and Triamcinolone via C6 transforaminal epidural inj under fluoroscopic guidance. Hx of chronic cervical pain and multilevel degenerative disc dz with multiple posterior disc protrusion on cervical imaging. Approximately 15 min post-procedure, pt noted weakness in left arm and bilateral lower limbs. F/u 24 hour MRI showed patchy increased T2 and short tau inversion in cervical cord, consistent with a diffuse vascular infarct to the cervical cord, resulting in motor-incomplete tetraplegia. No direct cord trauma occurred.
Undetermined	Triamcinolone	1915477	Epidural	NR	NR	Neck pain	Quadriplegia	74 yo F pt received Aristocort and Marcaine via epidural for neck pain in (b) (6). 7 min later, pt found slumped in chair, respiratory arrest and possible cardiac arrest. Pt intubated and tx with Dilantin. Pt in a coma (b) (6). At time of last f/u, pt regained some orientation, but still quadriplegic. MD suspects permanent disability.

IT: intrathecal; NR: not reported; yo: year old; M: male; F: female; pt: patient; dz: disease; inj: injection.

9.3 AERS ISR NUMBERS

Betamethasone	Dexamethasone	Methylprednisolone	Triamcinolone
1638328	320904	622077	6407456
3168014	1729909	5186580	4701577
4946477		1608973	5946840
5194750		1994376	6463890
		3288586	1915477
		1523055	4493127
		4144187	1795939
		5555955	

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 14, 2011

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Subject: Catastrophic Neurologic Events with Epidural Administration of:

Drug Name(s): Bupivacaine, Lidocaine, Ropivacaine, Fentanyl, Iohexol,
Gadodiolamide, Morphine, and Clonidine

NDA/ANDA: 16-964, 88-325, 20-533, 19-101, 18-956, 20-123, 18-565/21-671,
and 20-615

TSI #: 822

OSE RCM #: 2010-2231

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1 INTRODUCTION

This brief review provides a summary of Adverse Event Reporting System (AERS) data and safety related labeling information for a limited number of catastrophic neurologic events (cerebral vascular accident, cerebral infarction, cerebellar infarction, quadriplegia, paraplegia, and spinal cord infarction) reported for a sample of local anesthetics, contrast agents, analgesics, and clonidine administered epidurally; it is a follow-up to our May 2010 safety review of epidural corticosteroids and central nervous system adverse events (see Background).

2 BACKGROUND

This review was requested by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to provide supplemental information and context to the prior DPV-II safety review (OSE RCM #: 2009-2228; May 14, 2010) of catastrophic neurologic events reported with transforaminal epidural administration of corticosteroids for perineural infiltration for neck and back pain.

The May 2010 review found AERS and literature cases of catastrophic neurologic events reported during, or within 48 hours, of transforaminal epidural administration of three representative particulate steroids (hydrocortisone, methylprednisolone, triamcinolone) and two representative non-particulate steroids (betamethasone, dexamethasone). Data from that review suggested that catastrophic neurologic events were reported with epidural injections including, but not limited to, transforaminal administration of both particulate steroids and non-particulate corticosteroids, with death noted for particulate corticosteroids only. The review supported inadvertent intravascular administration as a factor in many of the cases. As described in the prior review, in addition to the documented role of procedural trauma (such as needle trauma to vertebral and peri-spinal vessels and peri-vascular/peri-spinal hematoma), limited animal data suggests that introduction of particulate steroids directly into the vertebral arteries may have an etiologic role in causing anterograde microemboli in areas cephalad to needle insertion (e.g., brain stem, midbrain, and cerebrum). It may, therefore, be postulated that *some* cases of adverse neurologic events reported in humans may be due to this mechanism. Additionally, since the May 2010 review, DPV-II has become aware of preclinical data suggesting that tissue injury may be due to preparation excipients.^{1,2,3}

A Drug Safety Board discussion of a proposed Drug Safety Communication based on the above review prompted a DPARP request of DPV II for a “high-level” AERS assessment for catastrophic neurologic events with other commonly administered epidural drugs. DPARP and DPV-II jointly agreed to limit the scope of this review to a sample of commonly used anesthetics (bupivacaine, lidocaine, and ropivacaine), contrast agents (gadodiamide and iohexol), analgesics (fentanyl and morphine), and clonidine.

¹ Benzon HT, Chew TL, McCarty RJ, Benzon HA, Walega DR. Comparison of the particle size of different steroids and the effect of dilution. A review of the relative neurotoxicity of the steroids. *Anesthesiology* 2007; 106:331-338

² Benzon HT, Gissen AJ, Strichartz GR, Avram MJ, Covino BG: The effect of polyethylene glycol on mammalian nerve impulses. *Anesth Analg* 1987; 66:553-9

³ Craig DB, Habib GG: Flaccid paraparesis following obstetrical epidural anesthesia: Possible role of benzyl alcohol. *Anesth Analg* 1977; 56:219-22

3 MATERIAL REVIEWED

AERS: DPV-II limited its AERS search to the most common serious neurologic adverse events noted in the prior review. Searches were performed by active ingredient name, restricted to serious outcomes, with the following Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PT): cerebrovascular accident, cerebral infarction, cerebellar infarction, quadriplegia, paraplegia, spinal cord infarction. An attempt was made to limit the route of administration to epidural and intra-arterial to enhance detection of reports coded according to unintended route of administration. The cut-off date for reports received in AERS was November 1, 2010.

Labels: Label reviews were limited to the best representative label(s) for each drug (by active ingredient) where such product is indicated for epidural use.

Literature: A comprehensive literature review was deemed unnecessary in view of the paucity of unconfounded AERS cases and the current labeling status of each drug (see Table 1). A limited literature survey yielded several relevant articles (summarized in section 5).

4 RESULTS

All cases were reviewed by the Medical Reviewer in order to determine potential clinical relevance. Table 1 summarizes the crude count (any PT of interest), de-duplicated/unique cases, and cases determined to be possibly informative based on all clinical information provided. All possibly relevant cases were found in the anesthetic group (N=3).

Table 1: AERS Case Summary and Label Summary

Drug	Crude Count	Unique Cases ¹	Possible Cases ²	Regulatory submission/Label
Anesthetics				
Ropivacaine	10	10	0	NDA 20-533: <u>Labeled</u> for epidural administration (continuous & bolus); Safety labeling for temporary and permanent neurologic sequelae are in Adverse Reactions (Neurologic). Specifically “spinal block”, “paresthesia”, “paralysis of the lower extremities”.
Lidocaine	28	27	0	ANDA 88-325: as above
Bupivacaine	61	57	3	NDA 16-964: as above and
Imaging Agents				
Iohexol	6	6	0	NDA 18-956: <u>Labeled</u> for intravascular and intrathecal use; Safety labeling for neurologic sequelae including cerebral hemorrhage.
Gadodiamide	0	--	--	NDA 20-123: <u>Labeled</u> for intravenous but NOT FOR INTRATHECAL use; Safety labeling for sensory and motor neurologic events Warnings and Precautions.
Analgesics				
Fentanyl	18	14	0	ANDA 19-101: <u>Labeled</u> for regional anesthesia; No safety labeling for neurologic events, not for co-administration with MAO inhibitors (potential for hypertensive crisis).
Morphine	7	7	0	NDA 18-565: (Duramorph): <u>Labeled</u> for intravenous, epidural, and intrathecal; Labeled for coma and seizures from drug effect and drug-drug interaction. NDA 21-671: (DepoDur): <u>Labeled</u> for lumbar epidural use, but not for intrathecal, intravenous, or intramuscular use. Labeled for coma and seizures from drug effect and drug-drug interaction.
Other				
Clonidine	4	2	0	NDA 20-615: <u>Labeled</u> for epidural treatment of neuropathic pain; not indicated for obstetric use or peri-operative pain management; Labeled for hypotension and coma notably in overdose.

¹De-duplication by comparison of demographic and narrative characteristics.

²Adequate clinical information to assess, and excludes illegible reports and confounders such as: epidural co-administration of corticosteroids and other non-steroid drugs, confirmed intra-operative hypotension, confirmed epidural hematoma, spinal trauma, arachnoiditis, documented procedure error (such as inadvertent spinal placement), or systemic anticoagulants or anti-platelet drugs.

A thorough review of all unique cases indicates that in almost all cases, factors such as epidural infusion of multiple drugs, epidural hematoma, identifiable trauma, and inadvertent intrathecal administration preclude assessment of the role of any particular drug.

The three possible cases (adequate information to assess and no obvious confounders), all in patients receiving single agent bupivacaine include:

- A 19-year old woman received epidural bupivacaine for a cesarean section delivery of an uncomplicated pregnancy. She experienced paraplegia within 24 hours of the procedure; duration unknown with no recovery at the time of receipt of report by the manufacturer (approximately 4 months). She received bupivacaine 0.75% which is above the currently labeled concentration for obstetric use. (ISR #: 387687)

- A 70-year old woman received epidural bupivacaine for an abdominal hysterectomy for uterine cancer. She experienced post-procedural paraparesis with subsequent documentation of slow femoral nerve conduction. The concentration of bupivacaine was not provided. Patient was discharged from rehabilitation center to nursing home with persistent weakness; exact duration of event unspecified. (ISR #: 432103)
- A 79-year old woman received epidural bupivacaine for an uncomplicated right hip arthroplasty. Approximately 2 hours after surgery continuous epidural infusion of bupivacaine 0.25% was started. One day later she developed lower extremity paraplegia and paresthesia. There was no documented anatomic injury with computed tomography and myelography at week 4 after symptoms began. Symptoms persisted at least 4 weeks (end of clinical narrative). (ISR #: 875243)

5 LITERATURE

Two large surveys of anesthesia literature, an adverse event report for Iohexol, and a retrospective case series for gadodiamide are described below.

In a 6-year Finnish study of severe complications with epidural and spinal anesthesia based on claims review, Aromaa reports 25 serious complications in 550,000 spinal anesthesia procedures and 9 serious complications in 170,000 epidural procedures.⁴ Serious complications in the epidural group included paraparesis (1), permanent cauda equina syndrome (1), peroneal nerve paresis (1), neurological deficit (1), bacterial infections (2), acute toxic reactions related to the anesthetic solution (2), and overdose of epidural opioid (1). They conclude that serious complications were reported in 0.45/10,000 spinal anesthetic procedures and 0.52/10,000 epidural anesthetic procedures.

The Royal College of Anaesthetists reports 293,050 instances of epidural anesthesia in a total of 707,425 cases of “central neuraxial block” (e.g., spinal or epidural anesthesia).⁵ Adverse outcomes were estimated by strict clinical criteria which allowed greater exclusions for inadequate data (“optimistic”) and by less strict criteria (“pessimistic”). The optimistic estimate is lower and the pessimistic estimate is higher. For epidural anesthesia, the incidence estimate for permanent harm not-otherwise-specified is 3.1 to 6.1/100,000, and the incidence estimate for paraplegia or death is 0.3 to 2.0/100,000.

Safriel reports outcomes in 304 patients who underwent 527 injection of gadodiamide/gadolinium.⁶ Of this group, 171 patients had epidural co-administration of corticosteroid for pain management, and 11 patients had facet injection with co-administration of corticosteroid. Serious adverse events were limited to seizures in two patients. One patient received a discogram without steroid. The other was a patient who received inter-laminar contrast with corticosteroid. Both patients recovered and were discharged in 2 to 3 days without sequelae.

Lee reports a 55-year old male who presented for transforaminal corticosteroid injection at C6-7 under fluoroscopic guidance and experienced quadriplegia presumed to be due to introduction of

⁴ Aromaa U, Lahdensuu M, Cozantis DA. Severe complications associated with epidural and spinal anaesthesias in Finland 1987-1993. A study based on patient insurance claims. *Acta Anaesthesiol Scand* 1997; 41:445-452.

⁵ Cook TM, Counsell D, Wildsmith JAW., et. al., Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *British Journal of Anaesthesia* 2009; 102(2):179-190.

⁶ Safriel Y, Ang R., Ali M. Gadolinium use in spine pain management procedures for patients with contrast allergies: Results in 527 procedures. *Cardiovasc Intervent Radiol* 2008; 31:325-331. (Comment: retracted for prior submission of a portion of data in another publication, not for data integrity).

intra-spinal air with Iohexol injection.⁷ The event occurred prior to corticosteroid injection. One year later, motor paraparesis improved and was limited to his left arm/hand.

No other relevant articles were retrieved.

6 DISCUSSION

AERS data and literature suggest that the occurrence of catastrophic neurologic events of the type seen in our May 2010 review of epidural corticosteroids (OSE RCM #: 2009-2228; May 14, 2010) appears low with epidural administration of the drugs discussed in this review, particularly when confounders such as procedural trauma are excluded. Additionally, the drugs discussed in this review are labeled for intravascular use and epidural use (with the exception of Depodur (morphine sulfate injection, lipid complex) which is not indicated for intravenous use and which may be administered as a single dose epidurally at the lumbar level only)

These findings differ with catastrophic neurologic events reported with transforaminal steroid injections discussed in our prior review in that corticosteroids are not labeled for epidural administration (transforaminal or non-transforaminal). Literature presented in the prior review show that corticosteroids such as methylprednisolone acetate are used for off-label for transforaminal injections; labeling does, however, specify “not for intravenous use,” and at least one formulation (methylprednisolone acetate, NDA 11-757) specifically contraindicates for intrathecal use, noting arachnoiditis, paraparesis, and paraplegia with intrathecal/epidural administration.

Lastly, a comparison of event rates between corticosteroids and the drugs discussed in this review could not be performed with AERS data due to limitations of postmarketing data and differences in labeling across the products reviewed. Such comparisons were not found in the literature.

7 CONCLUSIONS

In conclusion, a focused AERS search for a limited set of catastrophic neurologic events reported with epidural administration of a variety of local anesthetics, contrast agents, analgesics, and clonidine revealed a small number of unconfounded cases. Available literature shows a relatively small number of mentions for catastrophic neurologic events for local anesthetics, no catastrophic neurological events for gadodiamide/gadolinium, and one serious adverse event with Iohexol that was documented to be due to mechanical trauma. Overall, this assessment does not show a pattern for catastrophic neurologic adverse events with these drugs analogous to that observed with epidural corticosteroid use (based on our May 2010 review). Additionally, we note that serious CNS events with epidural use of the drugs in this review are frequently labeled, in contrast to corticosteroids.

⁷ Lee JH, Lee JK, Seo BR, Moon SJ, et. al., Spinal cord injury produced by direct damage during cervical transforaminal epidural injection. *Reg Anesth Pain Med* 2008;33:377-379.

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/s/

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02/15/2011

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CELESTONE[®] SOLUSPAN^{®*}

brand of

betamethasone sodium phosphate

and betamethasone acetate Injectable Suspension USP

6 mg per mL

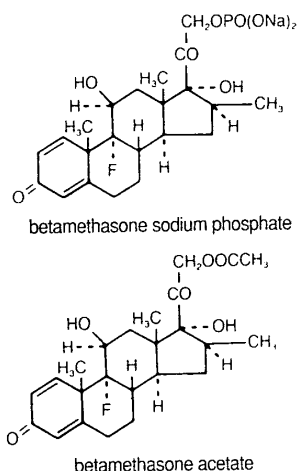
*brand of rapid and repository injectable

DESCRIPTION CELESTONE[®] SOLUSPAN^{®*} Injectable Suspension is a sterile aqueous suspension containing 3 mg per milliliter betamethasone, as betamethasone sodium phosphate, and 3 mg per milliliter betamethasone acetate. Inactive ingredients per mL: 7.1 mg dibasic sodium phosphate; 3.4 mg monobasic sodium phosphate; 0.1 mg edetate disodium; and 0.2 mg benzalkonium chloride as preservative. The pH is adjusted to between 6.8 and 7.2.

The formula for betamethasone sodium phosphate is $C_{22}H_{28}FNa_2O_8P$ and it has a molecular weight of 516.40. Chemically, it is 9-Fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 21-(disodium phosphate).

The formula for betamethasone acetate is $C_{24}H_{31}FO_6$ and it has a molecular weight of 434.50. Chemically, it is 9-Fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 21-acetate.

The chemical structures for betamethasone sodium phosphate and betamethasone acetate are as follows:



Betamethasone sodium phosphate is a white to practically white, odorless powder, and is hygroscopic. It is freely soluble in water and in methanol, but is practically insoluble in acetone and in chloroform.

Betamethasone acetate is a white to creamy white, odorless powder that sinters and resolidifies at about 165°C, and remelts at about 200°C-220°C with decomposition. It is practically insoluble in water, but freely soluble in acetone, and is soluble in alcohol and in chloroform.

CLINICAL PHARMACOLOGY Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems. A derivative of prednisolone, betamethasone has a 16β-methyl group that enhances the anti-inflammatory action of the molecule and reduces the sodium- and water-retaining properties of the fluorine atom bound at carbon 9.

Betamethasone sodium phosphate, a soluble ester, provides prompt activity, while betamethasone acetate is only slightly soluble and affords sustained activity.

INDICATIONS AND USAGE When oral therapy is not feasible, the **intramuscular use** of CELESTONE[®] SOLUSPAN^{®*} Injectable Suspension is indicated as follows:

Allergic States Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic Diseases Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders Congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Hydrocortisone or cortisone is the drug of choice in primary or secondary adrenocortical insufficiency. Synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance.

Gastrointestinal Diseases To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic Disorders Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

Miscellaneous Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic Diseases For palliative management of leukemias and lymphomas.

Nervous System Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor or craniotomy.

Ophthalmic Diseases Sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal Diseases To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory Diseases Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic Disorders As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

The **intra-articular or soft tissue administration** of CELESTONE SOLUSPAN Injectable Suspension is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

The **intralesional administration** of CELESTONE SOLUSPAN Injectable Suspension is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques; necrobiosis lipoidica diabetorum.

CELESTONE SOLUSPAN Injectable Suspension may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS CELESTONE[®] SOLUSPAN^{®*} Injectable Suspension is contraindicated in patients who are hypersensitive to any components of this product.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

WARNINGS CELESTONE[®] SOLUSPAN^{®*} Injectable Suspension should not be administered intravenously.

Serious Neurologic Adverse Reactions with Epidural Administration Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).

In patients on corticosteroid therapy subjected to any unusual stress, hydrocortisone or cortisone is the drug of choice as a supplement during and after the event.

Cardio-renal Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine Corticosteroids can produce reversible hypothalamic pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections *General* Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of

amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **PRECAUTIONS, Drug Interactions, *Amphotericin B Injection and Potassium-Depleting Agents*** section).

Special Pathogens Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or

inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, eg, for Addison's disease.

Viral Infections Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.

Neurologic Reports of severe medical events have been associated with the intrathecal route of administration (see **ADVERSE REACTIONS, Gastrointestinal and Neurologic/Psychiatric** sections).

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early mortality (at 2 weeks) and late mortality (at 6 months) in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of corticosteroids, including CELESTONE SOLUSPAN, should not be used for the treatment of traumatic brain injury.

Ophthalmic Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may

lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS General This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-renal As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy. Therefore, in any situation of stress occurring during that period, naturally occurring glucocorticoids (hydrocortisone cortisone), which also have salt-retaining properties, rather than betamethasone, are the appropriate choices as replacement therapy in adrenocortical deficiency states.

Gastrointestinal Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Intra-Articular and Soft Tissue Administration Intra-articular injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously injected joint is not usually recommended.

Corticosteroid injection into unstable joints is generally not recommended.

Intra-articular injection may result in damage to joint tissues (see **ADVERSE REACTIONS, Musculoskeletal** section).

Musculoskeletal Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (ie, decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a

decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (ie, postmenopausal women) before initiating corticosteroid therapy.

Neuro-psychiatric Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see **DOSAGE AND ADMINISTRATION**).

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical

attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions ***Aminoglutethimide*** Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B Injection and Potassium-Depleting Agents When corticosteroids are administered concomitantly with potassium-depleting agents (ie, amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, Oral Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular Drugs Serum concentrations of isoniazid may be decreased.

Cholestyramine Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis Glycosides Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, Including Oral Contraceptives Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (eg, barbiturates, phenytoin, carbamazepine, rifampin) Drugs which induce hepatic microsomal drug-metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Ketoconazole Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal Anti-inflammatory Agents (NSAIDs) Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin Tests Corticosteroids may suppress reactions to skin tests.

Vaccines Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Route administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS, Infections, *Vaccination*** section).

Carcinogenesis, Mutagenesis, Impairment of Fertility No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy *Teratogenic Effects* *Pregnancy Category C* Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Pediatric Use The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and

safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, eg, severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (ie, cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Geriatric Use No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and young patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS (listed alphabetically, under each subsection) **Allergic Reactions** Anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine Decreased carbohydrate and glucose tolerance, development of cushingoid state, glucosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic Negative nitrogen balance due to protein catabolism.

Musculoskeletal Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare

(following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see **WARNINGS, Neurologic** section).

Ophthalmic Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE Treatment of acute overdose is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION Benzyl alcohol as a preservative has been associated with a fatal “Gasping Syndrome” in premature infants and infants of low birth weight. Solutions used for further dilution of this product should be preservative-free when used in the neonate, especially the premature infant. The initial dosage of parenterally administered CELESTONE[®] SOLUSPAN^{®*} Injectable Suspension may vary from 0.25 to 9.0 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administrations in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

It Should Be Emphasized That Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 30 mg of betamethasone for a week followed by 12 mg every other day for 1 month are recommended (see **PRECAUTIONS, Neuro-psychiatric** section).

In pediatric patients, the initial dose of betamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02 to 0.3 mg/kg/day in three or four divided doses (0.6 to 9 mg/m²bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

If coadministration of a local anesthetic is desired, CELESTONE SOLUSPAN Injectable Suspension may be mixed with 1% or 2% lidocaine hydrochloride, using the formulations which do not contain parabens. Similar local anesthetics may also be used. Diluents containing methylparaben, propylparaben, phenol, etc., should be avoided, since these compounds may cause flocculation of the steroid. The required dose of CELESTONE SOLUSPAN Injectable Suspension is first withdrawn from the vial into the syringe. The local anesthetic is then drawn in, and the syringe shaken briefly. **Do not inject local anesthetics into the vial of CELESTONE SOLUSPAN Injectable Suspension.**

Bursitis, Tenosynovitis, Peritendinitis In acute subdeltoid, subacromial, olecranon, and prepatellar bursitis, one intrabursal injection of 1.0 mL CELESTONE SOLUSPAN Injectable Suspension can relieve pain and restore full range of movement. Several intrabursal injections of corticosteroids are usually required in recurrent acute bursitis and in acute exacerbations of chronic bursitis. Partial relief of pain and some increase in mobility can be expected in both conditions after one or two injections. Chronic bursitis may be treated with reduced dosage once the acute condition is controlled. In tenosynovitis and tendinitis, three or four local injections at intervals of 1 to 2 weeks between injections are given in most cases. Injections should be made into the affected tendon sheaths rather than into the tendons themselves. In ganglions of joint capsules and tendon sheaths, injection of 0.5 mL directly into the ganglion cysts has produced marked reduction in the size of the lesions.

Rheumatoid Arthritis and Osteoarthritis Following intra-articular administration of 0.5 to 2.0 mL of CELESTONE SOLUSPAN Injectable Suspension, relief of pain, soreness, and stiffness may be experienced. Duration of relief varies widely in both diseases. Intra-articular Injection of CELESTONE SOLUSPAN Injectable Suspension is well

tolerated in joints and periarticular tissues. There is virtually no pain on injection, and the “secondary flare” that sometimes occurs a few hours after intra-articular injection of corticosteroids has not been reported with CELESTONE SOLUSPAN Injectable Suspension. Using sterile technique, a 20- to 24-gauge needle on an empty syringe is inserted into the synovial cavity and a few drops of synovial fluid are withdrawn to confirm that the needle is in the joint. The aspirating syringe is replaced by a syringe containing CELESTONE SOLUSPAN Injectable Suspension and injection is then made into the joint.

Recommended Doses for Intra-articular Injection

Size of joint	Location	Dose (mL)
Very large	Hip	1.0-2.0
Large	Knee, ankle, shoulder	1.0
Medium	Elbow, wrist	0.5-1.0
Small (metacarpophalangeal, interphalangeal) (sternoclavicular)	Hand, chest	0.25-0.5

A portion of the administered dose of CELESTONE SOLUSPAN Injectable Suspension is absorbed systemically following intra-articular injection. In patients being treated concomitantly with oral or parenteral corticosteroids, especially those receiving large doses, the systemic absorption of the drug should be considered in determining intra-articular dosage.

Dermatologic Conditions In intralesional treatment, 0.2 mL/cm² of CELESTONE SOLUSPAN Injectable Suspension is injected intradermally (not subcutaneously) using a tuberculin syringe with a 25-gauge, ½-inch needle. Care should be taken to deposit a uniform depot of medication intradermally. A total of no more than 1.0 mL at weekly intervals is recommended.

Disorders of the Foot A tuberculin syringe with a 25-gauge, 3/4-inch needle is suitable for most injections into the foot. The following doses are recommended at intervals of 3 days to a week.

Diagnosis	CELESTONE SOLUSPAN Injectable Suspension Dose (mL)
Bursitis under heloma durum or heloma molle	0.25-0.5
under calcaneal spur	0.5
over hallux rigidus or digiti quinti varus	0.5
Tenosynovitis, periostitis of cuboid	0.5
Acute gouty arthritis	0.5-1.0

HOW SUPPLIED CELESTONE® SOLUSPAN®* Injectable Suspension, 5-mL multiple-dose vial; box of one (NDC 0085-0566-05).

SHAKE WELL BEFORE USING.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Protect from light.

Rx only

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

Manufactured by: Patheon UK Limited, Covingham, Swindon, Wiltshire, SN3 5BZ, United Kingdom

For patent information: www.merck.com/product/patent/home.html

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Revised: 05/2014

uspi-mk5166a-soi-1405r006

Dexamethasone Sodium Phosphate Injection, USP

For Intravenous or Intramuscular Use Only

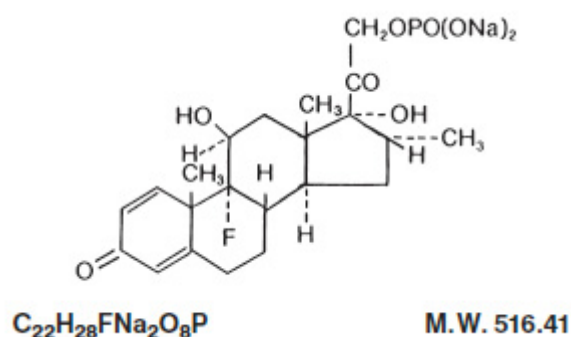
Rx only

DESCRIPTION

Dexamethasone Sodium Phosphate Injection, USP, is a water-soluble inorganic ester of dexamethasone which produces a rapid response even when injected intramuscularly.

Dexamethasone Sodium Phosphate, USP chemically is Pregna-1,4-diene-3,20-dione, 9-fluoro- 11,17-dihydroxy-16-methyl-21-(phosphonooxy)-, disodium salt, (11 β , 16 α).

It occurs as a white to creamy white powder, is exceedingly hygroscopic, is soluble in water and its solutions have a pH between 7.0 and 8.5. It has the following structural formula:



Each mL of Dexamethasone Sodium Phosphate Injection, USP (**Preservative Free**) contains dexamethasone sodium phosphate, USP equivalent to 10 mg dexamethasone phosphate; 24.75 mg sodium citrate, dihydrate; and Water for Injection, q.s. pH adjusted with citric acid or sodium hydroxide, if necessary. pH: 7.0 to 8.5.

Each mL Dexamethasone Sodium Phosphate Injection, USP (**Preserved**) contains dexamethasone sodium phosphate, USP equivalent to 10 mg dexamethasone phosphate; 13.5 mg sodium citrate, dihydrate; 10 mg benzyl alcohol; and Water for Injection, q.s. pH adjusted with citric acid or sodium hydroxide, if necessary. pH: 7.0 to 8.5.

CLINICAL PHARMACOLOGY

Dexamethasone sodium phosphate injection has a rapid onset but short duration of action when compared with less soluble preparations. Because of this, it is suitable for the treatment of acute disorders responsive to adrenocortical steroid therapy.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, including dexamethasone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property

of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

By intravenous or intramuscular injection when oral therapy is not feasible:

1. Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids

where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful.

Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.

Congenital adrenal hyperplasia

Nonsuppurative thyroiditis

Hypercalcemia associated with cancer

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Post-traumatic osteoarthritis

Synovitis of osteoarthritis

Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

Acute and subacute bursitis

Epicondylitis

Acute nonspecific tenosynovitis

Acute gouty arthritis

Psoriatic arthritis

Ankylosing spondylitis

3. Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of:

Systemic lupus erythematosus

Acute rheumatic carditis

4. Dermatologic Diseases

Pemphigus

Severe erythema multiforme (Stevens-Johnson syndrome)

Exfoliative dermatitis

Bullous dermatitis herpetiformis

Severe seborrheic dermatitis

Severe psoriasis

Mycosis fungoides

5. *Allergic States*

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma

Contact dermatitis

Atopic dermatitis

Serum sickness

Seasonal or perennial allergic rhinitis

Drug hypersensitivity reactions

Urticarial transfusion reactions

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

6. *Ophthalmic Diseases*

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus

Iritis, iridocyclitis

Chorioretinitis

Diffuse posterior uveitis and choroiditis

Optic neuritis

Sympathetic ophthalmia

Anterior segment inflammation

Allergic conjunctivitis

Keratitis

Allergic corneal marginal ulcers

7. *Gastrointestinal Diseases*

To tide the patient over a critical period of the disease in:

Ulcerative colitis (systemic therapy)

Regional enteritis (systemic therapy)

8. Respiratory Diseases

Symptomatic sarcoidosis

Berylliosis

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy.

Loeffler's syndrome not manageable by other means.

Aspiration pneumonitis

9. Hematologic Disorders

Acquired (autoimmune) hemolytic anemia.

Idiopathic thrombocytopenic purpura in adults

(IV only; IM administration is contraindicated).

Secondary thrombocytopenia in adults

Erythroblastopenia (RBC anemia)

Congenital (erythroid) hypoplastic anemia

10. Neoplastic Diseases

For palliative management of:

Leukemias and lymphomas in adults

Acute leukemia of childhood

11. Edematous States

To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

12. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Trichinosis with neurologic or myocardial involvement.

13. Diagnostic testing of adrenocortical hyperfunction.

14. *Cerebral Edema* associated with primary or metastatic brain tumor, craniotomy, or head injury. Use in cerebral edema is not a substitute for careful neurosurgical evaluation

and definitive management such as neurosurgery or other specific therapy.

CONTRAINDICATIONS

Systemic fungal infections (see **WARNINGS** regarding amphotericin B).

Hypersensitivity to any component of this product (see **WARNINGS**).

WARNINGS

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug. Anaphylactoid and hypersensitivity reactions have been reported for dexamethasone sodium phosphate injection (see **ADVERSE REACTIONS**).

Corticosteroids may exacerbate systemic fungal infections and, therefore, should not be used in the presence of such infections unless they are needed to control drug reactions due to amphotericin B. Moreover, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure.

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

Drug-induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results.

In cerebral malaria, a double-blind trial has shown that the use of corticosteroids is associated with prolongation of coma and a higher incidence of pneumonia and gastrointestinal bleeding.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Administration of live virus vaccines, including smallpox, is contraindicated in individuals receiving immunosuppressive doses of corticosteroids. If inactivated viral or bacterial vaccines are administered to individuals receiving immunosuppressive doses of corticosteroids, the expected serum antibody response may not be obtained. However, immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. The risk of developing a disseminated infection varies among individuals and can be related to the dose, route and duration of corticosteroid administration as well as to the underlying disease. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered. If exposed to

measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information).

The use of dexamethasone sodium phosphate injection in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Usage in Pregnancy

Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy or in women of childbearing potential requires that the anticipated benefits be weighed against the possible hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects. Mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

PRECAUTIONS

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including fever, myalgia, arthralgia, and malaise. This may occur in patients even without evidence of adrenal insufficiency.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used within caution in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving large doses of corticosteroids may be minimal or absent. Fat embolism has been reported as a possible complication of hypercortisonism.

When large doses are given, some authorities advise that antacids be administered between meals to help

prevent peptic ulcer.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. These interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs.

False negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies.

When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

The slower rate of absorption by intramuscular administration should be recognized.

Information for Patients

Susceptible patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Pediatric Use

Growth and development of infants and children patients on prolonged corticosteroid therapy should be carefully followed.

ADVERSE REACTIONS

Fluid and electrolyte disturbances:

- Sodium retention
- Fluid retention
- Congestive heart failure in susceptible patients
- Potassium loss
- Hypokalemic alkalosis
- Hypertension

Musculoskeletal:

- Muscle weakness
- Steroid myopathy
- Loss of muscle mass
- Osteoporosis

Vertebral compression fractures

Aseptic necrosis of femoral and humeral heads

Tendon rupture

Pathologic fracture of long bones

Gastrointestinal:

Peptic ulcer with possible subsequent perforation and hemorrhage

Perforation of the small and large bowel; particularly in patients with inflammatory bowel disease

Pancreatitis

Abdominal distention

Ulcerative esophagitis

Dermatologic:

Impaired wound healing

Thin fragile skin

Petechiae and ecchymoses

Erythema

Increased sweating

May suppress reactions to skin tests

Burning or tingling, especially in the perineal area (after IV injection)

Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema

Neurologic:

Convulsions

Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment

Vertigo

Headache

Psychic disturbances

Endocrine:

Menstrual irregularities

Development of cushingoid state

Suppression of growth in pediatric patients

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetics

Hirsutism

Ophthalmic:

Posterior subcapsular cataracts

Increased intraocular pressure

Glaucoma

Exophthalmos

Retinopathy of prematurity

Metabolic:

Negative nitrogen balance due to protein catabolism

Cardiovascular:

Myocardial rupture following recent myocardial infarction (see **WARNINGS**)

Hypertrophic cardiomyopathy in low birth weight infants

Other:

Anaphylactoid or hypersensitivity reactions

Thromboembolism

Weight gain

Increased appetite

Nausea

Malaise

Hiccups

The following *additional* adverse reactions are related to parenteral corticosteroid therapy:

Hyperpigmentation or hypopigmentation

Subcutaneous and cutaneous atrophy

Sterile abscess

Charcot-like arthropathy

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

The oral LD₅₀ of dexamethasone in female mice was 6.5 g/kg. The intravenous LD₅₀ of dexamethasone sodium phosphate in female mice was 794 mg/kg.

DOSAGE AND ADMINISTRATION

Dexamethasone sodium phosphate injection, 10 mg/mL— *For intravenous and intramuscular injection only.*

Dexamethasone sodium phosphate injection can be given directly from the vial, or it can be added to Sodium Chloride Injection or Dextrose Injection and administered by intravenous drip.

Solutions used for intravenous administration or further dilution of this product should be preservative free when used in the neonate, especially the premature infant.

When it is mixed with an infusion solution, sterile precautions should be observed. Since infusion solutions generally do not contain preservatives, mixtures should be used within 24 hours.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.

Intravenous and Intramuscular Injection

The initial dosage of dexamethasone sodium phosphate injection varies from 0.5 to 9 mg a day depending on the disease being treated. In less severe diseases doses lower than 0.5 mg may suffice, while in severe diseases doses higher than 9 mg may be required.

The initial dosage should be maintained or adjusted until the patient's response is satisfactory. If a satisfactory clinical response does not occur after a reasonable period of time, discontinue dexamethasone sodium phosphate injection and transfer the patient to other therapy.

After a favorable initial response, the proper maintenance dosage should be determined by decreasing the initial dosage in small amounts to the lowest dosage that maintains an adequate clinical response.

Patients should be observed closely for signs that might require dosage adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, individual drug responsiveness, and the effect of stress (e.g., surgery, infection, trauma). During stress it may be necessary to increase dosage temporarily. If the drug is to be stopped after more than a few days of treatment, it usually should be withdrawn gradually.

When the intravenous route of administration is used, dosage usually should be the same as the oral dosage. In certain overwhelming, acute, life-threatening situations, however, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages. The slower rate of absorption by intramuscular administration should be recognized.

Shock

There is a tendency in current medical practice to use high (pharmacologic) doses of corticosteroids for the treatment of unresponsive shock. The following dosages of dexamethasone sodium phosphate injection have been suggested by various authors:

<i>Author</i>	<i>Dosage</i>
Cavanagh ¹	3 mg/kg of body weight per 24 hours by constant intravenous infusion after an initial intravenous injection of 20 mg
Dietzman ²	2 to 6 mg/kg of body weight as a single intravenous injection
Frank ³	40 mg initially followed by repeat intravenous injection every 4 to 6 hours while shock persists

Oaks ⁴	40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists
Schumer ⁵	1 mg/kg of body weight as a single intravenous injection

Administration of high dose corticosteroid therapy should be continued only until the patient's condition has stabilized and usually not longer than 48 to 72 hours.

Although adverse reactions associated with high dose, short term corticosteroid therapy are uncommon, peptic ulceration may occur.

Cerebral Edema

Dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by four mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with 2 mg two or three times a day may be effective.

Acute Allergic Disorders

In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:

Dexamethasone sodium phosphate injection, *first day*, 4 or 8 mg intramuscularly.

Dexamethasone tablets, 0.75 mg: *second and third days*, 4 tablets in two divided doses each day; *fourth day*, 2 tablets in two divided doses; *fifth and sixth days*, 1 tablet each day; *seventh day*, no treatment; *eighth day*, follow-up visit.

This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

HOW SUPPLIED

Dexamethasone Sodium Phosphate Injection, USP (**Preservative Free**) equivalent to 10 mg dexamethasone phosphate, is supplied in a single dose vial as follows:

Product No.	NDC No.	Strength	Vial Size
500601	63323-506-01	10 mg/mL	1 mL

Packaged in twenty-fives.

Dexamethasone Sodium Phosphate Injection, USP (**Preserved**) equivalent to 10 mg dexamethasone phosphate, is supplied in a multiple dose vial as follows:

Product	NDC	Strength	Vial Size
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No.	No.		
501610	63323-516-10	10 mg/mL	10 mL

Packaged in tens.

Vial stoppers do not contain natural rubber latex.

Storage

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Sensitive to heat. Do not autoclave.

Protect from freezing.

Protect from light.

Single dose vials—Store in container until time of use. Discard unused portion.

Multiple dose vials—Store in container until contents are used.

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3. Frank, E.: Clinical observations in shock and management (in: Shields, T.F., ed.: Symposium on current concepts and management of shock), *J. Maine Med. Ass.* 59: 195-200, Oct. 1968.
4. Oaks, W. W.; Cohen, H.E.: Endotoxin shock in the geriatric patient, *Geriat.* 22: 120-130, Mar. 1967.
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45955D

Revised: April 2008

PACKAGE LABEL - PRINCIPAL DISPLAY - Dexamethasone 1 mL Vial Label

NDC 63323-506-01

500601

DEXAMETHASONE SODIUM PHOSPHATE INJECTION, USP

10 mg/mL

For IV or IM Use Only Rx only

1 mL Single Dose Vial

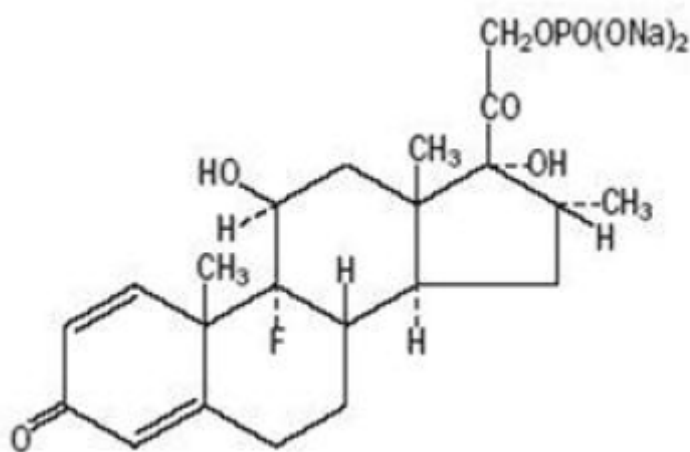
HEXADROL[®] PHOSPHATE INJECTION

(dexamethasone sodium phosphate injection, USP)

DESCRIPTION — Hexadrol[®] Phosphate Injection (dexamethasone sodium phosphate injection, USP) is a water-soluble inorganic ester of dexamethasone which produces a rapid response even when injected intramuscularly.

Dexamethasone Sodium Phosphate, $C_{22}H_{28}FNa_2O_8P$, has a molecular weight of 516.41 and chemically is Pregn-4-ene-3, 20-dione, 9-fluoro-11, 17-dihydroxy-16-methyl-21 (phosphonoxy)-, disodium salt, (11 β , 16 α).

It occurs as a white to creamy white powder, is exceedingly hygroscopic, is soluble in water and its solutions have a pH between 7.5 and 10.5. It has the following structural formula:



Hexadrol[®] Phosphate Injection is available in 4 mg/mL and 10 mg/mL concentrations.

Each mL of Hexadrol[®] Phosphate Injection 4 mg/mL, contains dexamethasone sodium phosphate, USP equivalent to 4 mg dexamethasone phosphate; 1 mg sodium sulfite; 10 mg benzyl alcohol (preservative). Made isotonic with sodium citrate. pH adjusted with citric acid or sodium hydroxide.

Each mL of Hexadrol® Phosphate Injection 10 mg/mL, contains dexamethasone sodium phosphate, USP equivalent to 10 mg dexamethasone phosphate; 1.5 mg sodium sulfite; 10 mg benzyl alcohol (preservative). Made isotonic with sodium citrate. pH adjusted with citric acid or sodium hydroxide.

ACTIONS — Naturally occurring glucocorticoids (hydrocortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS —

A. Intravenous or intramuscular administration. When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, those products labeled for intravenous or intramuscular use are indicated as follows:

1. **Endocrine disorders.** Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance).

Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used).

Preoperatively, and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful. Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected.

Congenital adrenal hyperplasia.
Nonsuppurative thyroiditis.
Hypercalcemia associated with cancer.

2. *Rheumatic disorders.* As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Post-traumatic osteoarthritis.
Synovitis of osteoarthritis.
Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).
Acute and subacute bursitis.
Epicondylitis.
Acute nonspecific tenosynovitis.
Acute gouty arthritis.
Psoriatic arthritis.
Ankylosing spondylitis.

3. *Collagen diseases. During an exacerbation or as maintenance therapy in selected cases of:*

Systemic lupus erythematosus.
Acute rheumatic carditis.

4. *Dermatologic diseases.*

Pemphigus.
Severe erythema multiforme (Stevens-Johnson Syndrome).
Exfoliative dermatitis.
Bullous dermatitis herpetiformis.
Severe seborrheic dermatitis.
Severe psoriasis.
Mycosis fungoides.

5. Allergic states. Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:

Bronchial asthma.

Contact dermatitis.

Atopic dermatitis.

Serum sickness.

Seasonal or perennial allergic rhinitis.

Drug hypersensitivity reactions.

Urticarial transfusion reactions.

Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

6. Ophthalmic diseases. Severe acute and chronic allergic and inflammatory processes involving the eye, such as:

Herpes zoster ophthalmicus.

Iritis, iridocyclitis.

Chorioretinitis.

Diffuse posterior uveitis and choroiditis.

Optic neuritis.

Sympathetic ophthalmia.

Anterior segment inflammation.

Allergic conjunctivitis.

Allergic corneal marginal ulcers.

Keratitis.

7. Gastrointestinal diseases. To tide the patient over a critical period of the disease in:

Ulcerative colitis (systemic therapy).

Regional enteritis (systemic therapy).

8. Respiratory diseases:

Symptomatic Sarcoidosis.

Berylliosis.

Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate anti-tuberculosis chemotherapy.

Loeffler's syndrome not manageable by other means.

Aspiration pneumonitis.

9. Hematologic disorders:

Acquired (autoimmune) hemolytic anemia.

Idiopathic thrombocytopenic purpura in adults (I.V. only; I.M. administration is contraindicated).

Secondary thrombocytopenia in adults.

Erythroblastopenia (RBC anemia).

Congenital (erythroid) hypoplastic anemia.

10. Neoplastic diseases. For palliative management of:

Leukemias and lymphomas in adults.

Acute leukemia of childhood.

11. Edematous states. To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.

12. Nervous system.

Acute exacerbations of multiple sclerosis.

13. Miscellaneous.

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate anti-tuberculosis chemotherapy.

Trichinosis with neurologic or myocardial involvement.

Diagnostic testing of adrenocortical hyperfunction.

Cerebral edema of diverse etiologies in conjunction with adequate neurological evaluation and management.

B. Intra-articular or soft tissue administration. When the strength and dosage form of the drug lend the preparation to the treatment of the condition, those products labeled for intra-articular or soft tissue administration are indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:

Synovitis of osteoarthritis.

Rheumatoid arthritis.

Acute and subacute bursitis.

Acute gouty arthritis.

Epicondylitis.

Acute nonspecific tenosynovitis.

Post-traumatic osteoarthritis.

C. Intralesional administration. When the strength and dosage form of the drug lend the preparation to the treatment of the condition, those products labeled for intralesional administration are indicated for:

Keloids.

Localized hypertrophic, infiltrated, inflammatory lesions of: lichen planus, psoriatic plaques, granuloma annulare, and lichen simplex chronicus (neurodermatitis).

Discoid lupus erythematosus.

Necrobiosis lipoidica diabetorum.

Alopecia areata.

They also may be useful in cystic tumors of an aponeurosis tendon (ganglia).

CONTRAINDICATIONS — Systemic fungal infections.

WARNINGS —

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

In patients on corticosteroid therapy subject to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may

be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Usage in Pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with a stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially in high doses, because of possible hazards of neurological complications and lack of antibody response.

The use of Hexadrol® Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Hexadrol® Phosphate Injection contains sodium sulfite, a sulfite that may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

PRECAUTIONS — Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs

and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See Dosage and Administration Section).

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

ADVERSE REACTIONS —

Fluid and electrolyte disturbances:

- Sodium retention
- Fluid retention
- Congestive heart failure in susceptible patients
- Potassium loss
- Hypokalemic alkalosis
- Hypertension

Musculoskeletal:

- Muscle weakness
- Steroid myopathy
- Loss of muscle mass
- Osteoporosis

Vertebral compression fractures
Aseptic necrosis of femoral and humeral heads
Pathologic fracture of long bones

Gastrointestinal:

Peptic ulcer with possible subsequent perforation and hemorrhage
Pancreatitis
Abdominal distention
Ulcerative esophagitis

Dermatological:

Impaired wound healing
Thin fragile skin
Facial erythema
Increased sweating
May suppress reactions to skin tests
Petechiae and ecchymoses

Neurological:

Convulsions
Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment
Vertigo
Headache

Ophthalmic:

Posterior subcapsular cataracts
Increased intraocular pressure
Glaucoma

Endocrine:

Menstrual irregularities

Development of cushingoid state

Suppression of growth in children

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness

Decreased carbohydrate tolerance

Manifestations of latent diabetes mellitus

Increased requirements for insulin or oral hypoglycemic agents in diabetics

Metabolic:

Negative nitrogen balance due to protein catabolism

Miscellaneous:

Hyperpigmentation or hypopigmentation

Subcutaneous and cutaneous atrophy

Sterile abscess

Postinjection flare, following intra-articular use

Charcot-like arthropathy

Itching, burning, tingling in the ano-genital region

DOSAGE AND ADMINISTRATION —

A. Intravenous or intramuscular administration. The initial dosage of Hexadrol® Phosphate Injection (dexamethasone sodium phosphate injection, USP) may vary from 0.50 mg/day to 9.0 mg/day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. Usually the parenteral dosage ranges are one-third to one-half the oral dose given every 12 hours. However, in certain overwhelming, acute, life-threatening situations, administration of dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

For the treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

For the treatment of cerebral edema in adults an initial intravenous dose of 10 mg is recommended followed by 4 mg intramuscularly every six hours until maximum response has been noted. This regimen may be continued for several days postoperatively in patients requiring brain surgery. Oral dexamethasone, 1 to 3 mg t.i.d., should be given as soon as possible and dosage tapered off over a period of five to seven days. Nonoperative cases may require continuous therapy to remain free of symptoms of increased intracranial pressure. The smallest effective dose should be used in children, preferably orally. This may approximate 0.2 mg/kg/24 hours in divided doses.

In treatment of acute exacerbations of multiple sclerosis daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day or 4–8 mg dexamethasone every other day for 1 month have been shown to be effective.

The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, Hexadrol® Phosphate Injection (dexamethasone sodium phosphate injection, USP) should be discontinued and the patient transferred to other appropriate therapy. It should be emphasized that dosage requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to

drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this later situation it may be necessary to increase the dosage of Hexadrol® Phosphate Injection (dexamethasone sodium phosphate injection, USP) for a period of time consistent with the patient's condition. If after a long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

B. Intra-articular, soft tissue or intralesional administration. The dose for intrasynovial administration is usually 2 to 4 mg for large joints and 0.8 to 1 mg for small joints. For soft tissue and bursal injections a dose of 2 to 4 mg is recommended. Ganglia require a dose of 1 to 2 mg. A dose of 0.4 to 1 mg is used for injection into tendon sheaths. Injection into intervertebral joints should not be attempted at any time and hip joint injection cannot be recommended as an office procedure.

Intrasynovial and soft tissue injections should be employed only when affected areas are limited to 1 or 2 sites. It should be remembered that corticoids provide palliation only and that other conventional or curative methods of therapy should be employed when indicated.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Frequency of injection usually ranges from once every 3 to 5 days to once every 2 to 3 weeks. Frequent intra-articular injection may cause damage to joint tissue.

HOW SUPPLIED —

- | | |
|---------------|---|
| 5-mL (4mg/mL) | multiple dose vial, NDC 0052-0796-05 |
| 5-mL (4mg/mL) | multiple dose vial, box of 25, NDC 0052-0796-27 |

10-mL (10mg/mL) vial, (for intravenous or intramuscular use only)

NDC 0052-0797-10

1-mL (4mg/mL) Prefilled Disposable Syringe, box of 25, NDC 0052-0796-26

1-mL (10mg/mL) Prefilled Disposable Syringe, box of 25, NDC 0052-0797-26

Protect from light. Store at 15°–30°C (59°–86°F).

CAUTION: Federal law prohibits dispensing without a prescription.

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SOLU-CORTEF®
(hydrocortisone sodium succinate for injection, USP)

NOT FOR USE IN NEONATES

CONTAINS BENZYL ALCOHOL

For Intravenous or Intramuscular Administration

DESCRIPTION

SOLU-CORTEF Sterile Powder is an anti-inflammatory glucocorticoid that contains hydrocortisone sodium succinate as the active ingredient. SOLU-CORTEF Sterile Powder is available in several packages for intravenous or intramuscular administration.

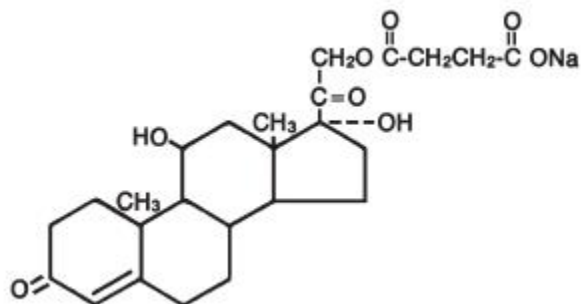
ACT-O-VIAL® System (Single-Dose Vial) in four strengths:

	100 mg	250 mg	500 mg	1000 mg
	ACT-O-VIAL	ACT-O-VIAL	ACT-O-VIAL	ACT-O-VIAL
	Each 2 mL	Each 2 mL	Each 4 mL	Each 8 mL
	contains (when	contains	contains	contains
	mixed):	(when mixed):	(when mixed):	(when mixed):
	equiv. to	equiv. to	equiv. to	equiv. to
	100 mg	250 mg	500 mg	1000 mg
	Hydrocortisone	Hydrocortisone	Hydrocortisone	Hydrocortisone
Hydrocortisone sodium succinate				
Monobasic sodium phosphate anhydrous	0.8 mg	2 mg	4 mg	8 mg
Dibasic sodium phosphate dried	8.73 mg	21.8 mg	44 mg	87.32 mg
Benzyl alcohol added as preservative	18.1 mg	16.4 mg	33.4 mg	66.9 mg

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8.

The chemical name for hydrocortisone sodium succinate is pregn-4-ene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-, monosodium salt, (11β)- and its molecular weight is 484.52.

The structural formula is represented below:



Hydrocortisone sodium succinate is a white or nearly white, odorless, hygroscopic amorphous solid. It is very soluble in water and in alcohol, very slightly soluble in acetone, and insoluble in chloroform.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. Thus, if constantly high blood levels are required, injections should be made every 4 to 6 hours. This preparation is also rapidly absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after intravenous injection.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

INDICATIONS AND USAGE

When oral therapy is not feasible, and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the **intravenous or intramuscular use** of SOLU-CORTEF Sterile Powder is indicated as follows:

Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis.

Hematologic disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond Blackfan anemia), idiopathic thrombocytopenic purpura in adults (intravenous administration only; intramuscular administration is contraindicated), pure red cell aplasia, select cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Neoplastic diseases: For the palliative management of leukemias and lymphomas.

Nervous System: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, or craniotomy.

Ophthalmic diseases: Sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, or that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy).

For the treatment of dermatomyositis, temporal arteritis, polymyositis, and systemic lupus erythematosus.

CONTRAINDICATIONS

SOLU-CORTEF Sterile Powder is contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

SOLU-CORTEF Sterile Powder is contraindicated for use in premature infants because the formulation contains benzyl alcohol. (See **WARNINGS** and **PRECAUTIONS: Pediatric Use**.)

SOLU-CORTEF Sterile Powder is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General:

This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **WARNINGS** and **PRECAUTIONS: Pediatric Use**).

Injection of SOLU-CORTEF may result in dermal and/or subdermal changes forming depressions in the skin at the injection site. In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including SOLU-CORTEF, should not be used for the treatment of traumatic brain injury.

Cardio-renal:

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine:

Hypothalamic-pituitary adrenal (HPA) axis suppression. Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Infections

General:

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Corticosteroids may also mask some signs of current infection. Do not use intra-

articularly, intrabursally or for intratendinous administration for *local* effect in the presence of acute local infection.

Fungal infections:

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**, Amphotericin B injection and potassium-depleting agents).

Special pathogens:

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis:

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination:

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.

Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., for Addison's disease).

Viral infections:

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic:

Reports of severe medical events have been associated with the intrathecal route of administration (see **ADVERSE REACTIONS**, Neurologic/Psychiatric).

Ophthalmic:

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS**General:**

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial. The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-renal:

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine:

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Gastrointestinal:

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Musculoskeletal:

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Local injection of a steroid into a previously infected site is not usually recommended.

Neurologic-psychiatric:

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic

manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic:

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients:

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions:

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see **PRECAUTIONS: Drug Interactions**, Hepatic Enzyme Inhibitors).

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs that induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin): Drugs that inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole: Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS: Infections, Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women.

Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

This product contains benzyl alcohol as a preservative.

Benzyl alcohol can cross the placenta. See PRECAUTIONS: Pediatric use.

Nursing Mothers:

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to continue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product ordinarily delivers amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age) and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids (e.g., severe asthma and wheezing) are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults

(see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Geriatric Use:

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported with SOLU-CORTEF or other corticosteroids:

Allergic reactions: Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, burning or tingling (especially in the perineal area, after intravenous injection), cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral

hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see **WARNINGS: Neurologic**).

Ophthalmic: Exophthalmoses, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see **WARNINGS**), malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdose is by supportive and symptomatic therapy. For chronic overdose in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see WARNINGS and PRECAUTIONS: Pediatric Use)

Because of possible physical incompatibilities, SOLU-CORTEF should not be diluted or mixed with other solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. This preparation may be administered by intravenous injection, by intravenous infusion, or by intramuscular injection, the preferred method for initial emergency use being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

Therapy is initiated by administering SOLU-CORTEF Sterile Powder intravenously over a period of 30 seconds (e.g., 100 mg) to 10 minutes (e.g., 500 mg or more). In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized, usually not beyond 48 to 72 hours. When high dose hydrocortisone therapy must be continued beyond 48–72 hours, hypernatremia may occur. Under such circumstances, it may be desirable to replace SOLU-CORTEF with a corticoid such as methylprednisolone sodium succinate which causes little or no sodium retention.

The initial dose of SOLU-CORTEF Sterile Powder is 100 mg to 500 mg, depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

This dose may be repeated at intervals of 2, 4, or 6 hours as indicated by the patient's response and clinical condition.

It Should Be Emphasized that Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that maintains an adequate clinical response is reached. Situations that may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation, it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 800 mg of hydrocortisone for a week followed by 320 mg every other day for one month are recommended (see **PRECAUTIONS, Neurologic-psychiatric**).

In pediatric patients, the initial dose of hydrocortisone may vary depending on the specific disease entity being treated. The range of initial doses is 0.56 to 8 mg/kg/day in three or four divided doses (20 to 240 mg/m²bsa/day). For the purpose of comparison, the

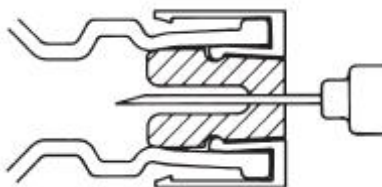
following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.
5. Insert needle **squarely through center** of stopper until tip is just visible. Invert vial and withdraw dose.



Further dilution is not necessary for intravenous or intramuscular injection. For intravenous infusion, first prepare solution as just described. The **100 mg** solution may then be added to 100 to 1000 mL of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction). The **250 mg** solution may be added to 250 to 1000 mL, the **500 mg** solution may be added to 500 to 1000 mL, and the **1000 mg** solution to 1000 mL of the same diluents. In cases where administration of a small volume of fluid is desirable, 100 mg to 3000 mg of SOLU-CORTEF may be added to 50 mL of the above diluents. The resulting solutions are stable for at least 4 hours and may be administered either directly or by IV piggyback.

When reconstituted as directed, pH's of the solutions range from 7 to 8 and the tonicities are: 100 mg ACT-O-VIAL, 0.36 osmolar; 250 mg ACT-O-VIAL, 500 mg ACT-O-VIAL, and 1000 mg ACT-O-VIAL, 0.57 osmolar. (Isotonic saline=0.28 osmolar.)

HOW SUPPLIED

SOLU-CORTEF Sterile Powder is available in the following packages:

100 mg ACT-O-VIAL (Single-Dose Vial)	250 mg ACT-O-VIAL (Single-Dose Vial)
2 mL—NDC 0009-0900-13	2 mL—NDC 0009-0909-08

25 x 2 mL—NDC 0009-0900-20

25 x 2 mL—NDC 0009-0909-16

500 mg ACT-O-VIAL (Single-Dose Vial)—NDC 0009-0912-05

1000 mg ACT-O-VIAL (Single-Dose Vial)—NDC 0009-0920-03

STORAGE CONDITIONS

Store unconstituted product at controlled room temperature 20° to 25°C (68° to 77°F).

Store solution at controlled room temperature 20° to 25°C (68° to 77°F) and protect from light. Use solution only if it is clear. Unused solution should be discarded after 3 days.

This product's label may have been updated. For current full prescribing information please visit www.pfizer.com



LAB-0121-12.3

Revised July 2014

SOLU-CORTEF®

(hydrocortisone sodium succinate for injection, USP)

For Intravenous or Intramuscular Administration

DESCRIPTION

SOLU-CORTEF Sterile Powder is an anti-inflammatory glucocorticoid that contains hydrocortisone sodium succinate as the active ingredient. SOLU-CORTEF Sterile Powder is available in several packages for intravenous or intramuscular administration.

100 mg Plain—Vials containing hydrocortisone sodium succinate equivalent to 100 mg hydrocortisone, 0.8 mg monobasic sodium phosphate anhydrous, 8.73 mg dibasic sodium phosphate dried. SOLU-CORTEF 100 mg plain does not contain diluent (see **DOSAGE AND ADMINISTRATION, Preparation of Solutions**).

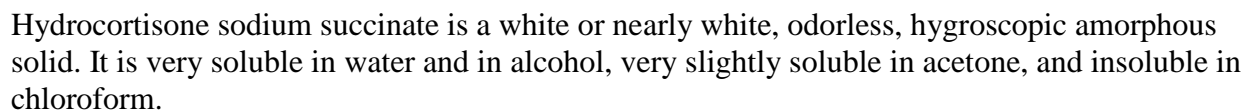
ACT-O-VIAL® System (Single-Dose Vial) in four strengths:

	100 mg ACT-O-VIAL Each 2 mL contains (when mixed): equiv. to 100 mg Hydrocortisone	250 mg ACT-O-VIAL Each 2 mL contains (when mixed): equiv. to 250 mg Hydrocortisone	500 mg ACT-O-VIAL Each 4 mL contains (when mixed): equiv. to 500 mg Hydrocortisone	1000 mg ACT-O-VIAL Each 8 mL contains (when mixed): equiv. to 1000 mg Hydrocortisone
Hydrocortisone sodium succinate				
Monobasic sodium phosphate anhydrous	0.8 mg	2 mg	4 mg	8 mg
Dibasic sodium phosphate dried	8.73 mg	21.8 mg	44 mg	87.32 mg

The diluent, as part of the packaging presentation for the ACT-O-VIAL® system, is comprised of Water for Injection only, and does not contain any preservative.

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8.

The chemical name for hydrocortisone sodium succinate is pregn-4-ene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-, monosodium salt, (11β)- and its molecular weight is 484.52.

[illegible]

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory actions as hydrocortisone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The highly water-soluble sodium succinate ester of hydrocortisone permits the immediate intravenous administration of high doses of hydrocortisone in a small volume of diluent and is particularly useful where high blood levels of hydrocortisone are required rapidly. Following the intravenous injection of hydrocortisone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. Thus, if constantly high blood levels are required, injections should be made every 4 to 6 hours. This preparation is also rapidly absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after intravenous injection.

INDICATIONS AND USAGE

When oral therapy is not feasible, and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the **intravenous or intramuscular use** of SOLU-CORTEF Sterile Powder is indicated as follows:

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hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis.

Hematologic disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond Blackfan anemia), idiopathic thrombocytopenic purpura in adults (intravenous administration only; intramuscular administration is contraindicated), pure red cell aplasia, select cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Neoplastic diseases: For the palliative management of leukemias and lymphomas.

Nervous System: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, or craniotomy.

Ophthalmic diseases: Sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, or that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, temporal arteritis, polymyositis, and systemic lupus erythematosus.

CONTRAINDICATIONS

SOLU-CORTEF Sterile Powder is contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

SOLU-CORTEF Sterile Powder is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General:

Injection of SOLU-CORTEF may result in dermal and/or subdermal changes forming depressions in the skin at the injection site. In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including SOLU-CORTEF, should not be used for the treatment of traumatic brain injury.

Cardio-renal:

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine:

Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use. Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Infections

General:

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection. Do not use intra-articularly, intrabursally, or for intratendinous administration for *local* effect in the presence of acute local infection.

Fungal infections:

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**, Amphotericin B injection and potassium-depleting agents).

Special pathogens:

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with

widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis:

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination:

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., for Addison's disease).

Viral infections:

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic:

Reports of severe medical events have been associated with the intrathecal route of administration (see **ADVERSE REACTIONS**, Neurologic/Psychiatric).

Ophthalmic:

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General:

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-renal:

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine:

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Gastrointestinal:

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Musculoskeletal:

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Local injection of a steroid into a previously infected site is not usually recommended.

Neurologic-psychiatric:

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic:

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients:

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions:

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see **PRECAUTIONS: Drug Interactions, Hepatic Enzyme Inhibitors**).

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs that induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin): Drugs that inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole: Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is

discontinued if possible (see **WARNINGS: Infections, Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers:

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to continue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age) and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids (e.g., severe asthma and wheezing) are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment

should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Geriatric Use:

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported with SOLU-CORTEF or other corticosteroids:

Allergic reactions: Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, burning or tingling (especially in the perineal area, after intravenous injection), cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see **WARNINGS: Neurologic**).

Ophthalmic: Exophthalmoses, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see **WARNINGS**), malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

Because of possible physical incompatibilities, SOLU-CORTEF should not be diluted or mixed with other solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

This preparation may be administered by intravenous injection, by intravenous infusion, or by intramuscular injection, the preferred method for initial emergency use being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

Therapy is initiated by administering SOLU-CORTEF Sterile Powder intravenously over a period of 30 seconds (e.g., 100 mg) to 10 minutes (e.g., 500 mg or more). In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized, usually not beyond 48 to 72 hours. When high dose hydrocortisone therapy must be continued beyond 48–72 hours, hypernatremia may occur. Under such circumstances, it may be desirable to replace SOLU-CORTEF with a corticoid such as methylprednisolone sodium succinate which causes little or no sodium retention.

The initial dose of SOLU-CORTEF Sterile Powder is 100 mg to 500 mg, depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

This dose may be repeated at intervals of 2, 4, or 6 hours as indicated by the patient's response and clinical condition.

It Should Be Emphasized that Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that maintains an adequate clinical response is reached. Situations that may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation, it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 800 mg of hydrocortisone for a week followed by 320 mg every other day for one month are recommended (see **PRECAUTIONS, Neurologic-psychiatric**).

In pediatric patients, the initial dose of hydrocortisone may vary depending on the specific disease entity being treated. The range of initial doses is 0.56 to 8 mg/kg/day in three or four divided doses (20 to 240 mg/m²bsa/day). For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

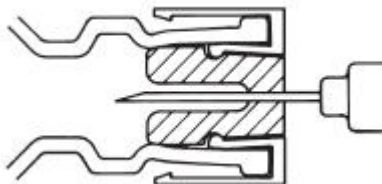
Preparation of Solutions:

100 mg Plain-For intravenous or intramuscular injection, prepare solution by aseptically adding **not more than 2 mL** of Bacteriostatic Water for Injection or Bacteriostatic Sodium Chloride Injection to the contents of one vial. **For intravenous infusion,** first prepare solution by adding **not more than 2 mL** of Bacteriostatic Water for Injection to the vial; this solution may then be added to 100 to 1000 mL of the following: 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction).

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.
5. Insert needle **squarely through center** of stopper until tip is just visible. Invert vial and withdraw dose.



Further dilution is not necessary for intravenous or intramuscular injection. For intravenous infusion, first prepare solution as just described. The **100 mg** solution may then be added to 100 to 1000 mL of 5% dextrose in water (or isotonic saline solution or 5% dextrose in isotonic saline solution if patient is not on sodium restriction). The **250 mg** solution may be added to 250 to 1000 mL, the **500 mg** solution may be added to 500 to 1000 mL, and the **1000 mg** solution to 1000 mL of the same diluents. In cases where administration of a small volume of fluid is desirable, 100 mg to 3000 mg of SOLU-CORTEF may be added to 50 mL of the above diluents. The resulting solutions are stable for at least 4 hours and may be administered either directly or by IV piggyback.

When reconstituted as directed, pH's of the solutions range from 7 to 8 and the tonicities are: 100 mg ACT-O-VIAL, 0.36 osmolar; 250 mg ACT-O-VIAL, 500 mg ACT-O-VIAL, and 1000 mg ACT-O-VIAL, 0.57 osmolar. (Isotonic saline=0.28 osmolar.)

HOW SUPPLIED

SOLU-CORTEF Sterile Powder is available in the following packages:

100 mg Plain—NDC 0009-0825-01

100 mg ACT-O-VIAL (Single-Dose Vial) **250 mg ACT-O-VIAL (Single-Dose Vial)**

2 mL—NDC 0009-0011-03

2 mL—NDC 0009-0013-05

25 x 2 mL—NDC 0009-0011-04

25 x 2 mL—NDC 0009-0013-06

500 mg ACT-O-VIAL (Single-Dose Vial)—NDC 0009-0016-12

1000 mg ACT-O-VIAL (Single-Dose Vial)—NDC 0009-0005-01

STORAGE CONDITIONS

Store unreconstituted product at controlled room temperature 20° to 25°C (68° to 77°F).

Store solution at controlled room temperature 20° to 25°C (68° to 77°F) and protect from light. Use solution only if it is clear. Unused solution should be discarded after 3 days.

This product's label may have been updated. For current full prescribing information please visit www.pfizer.com



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Division of Pfizer Inc
New York, NY 10017

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DEPO-MEDROL®

(methylprednisolone acetate injectable suspension, USP)

NOT FOR USE IN NEONATES CONTAINS BENZYL ALCOHOL

Not For Intravenous Use

DESCRIPTION

DEPO-MEDROL is an anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue, or intralesional injection. It is available in three strengths: 20 mg/mL, 40 mg/mL, 80 mg/mL.

Each mL of these preparations contains:

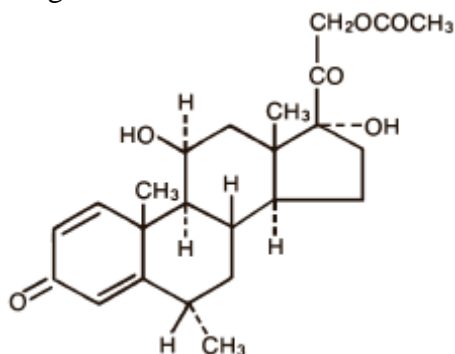
Methylprednisolone acetate.....	20 mg	40 mg	80 mg
Polyethylene glycol 3350.....	29.5 mg	29.1 mg	28.2 mg
Polysorbate 80	1.97 mg	1.94 mg	1.88 mg
Monobasic sodium phosphate	6.9 mg	6.8 mg	6.59 mg
Dibasic sodium phosphate USP.....	1.44 mg	1.42 mg	1.37 mg
Benzyl alcohol added as a preservative.....	9.3 mg	9.16 mg	8.88 mg

Sodium Chloride was added to adjust tonicity.

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

The pH of the finished product remains within the USP specified range (e.g., 3.5 to 7.0).

The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6 α ,11 β)- and the molecular weight is 416.51. The structural formula is represented below:



DEPO-MEDROL Sterile Aqueous Suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is a white or practically white, odorless, crystalline powder which melts at

about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, alcohol, chloroform, and methanol, and slightly soluble in ether. It is practically insoluble in water.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs are used primarily for their anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

INDICATIONS AND USAGE

A. FOR INTRAMUSCULAR ADMINISTRATION

When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the intramuscular use of DEPO-MEDROL Sterile Aqueous Suspension is indicated as follows:

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, seasonal or perennial allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic Diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis.

Hematologic Disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond Blackfan anemia), pure red cell aplasia, select cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Neoplastic Diseases: For palliative management of leukemias and lymphomas.

Nervous System: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor or craniotomy.

Ophthalmic Diseases: Sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal Diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, or that due to lupus erythematosus.

Respiratory Diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

B. FOR INTRA-ARTICULAR OR SOFT TISSUE ADMINISTRATION (See **WARNINGS**)

DEPO-MEDROL is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

C. FOR INTRALESIONAL ADMINISTRATION

DEPO-MEDROL is indicated for intralesional use in alopecia areata, discoid lupus erythematosus, keloids, localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques, necrobiosis lipoidica diabetorum. DEPO-MEDROL also may be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

DEPO-MEDROL is contraindicated in patients with known hypersensitivity to the product and its constituents.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

DEPO-MEDROL Sterile Aqueous Suspension is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

DEPO-MEDROL is contraindicated for use in premature infants because the formulation contains benzyl alcohol. (See **WARNINGS** and **PRECAUTIONS: Pediatric Use**.)

DEPO-MEDROL is contraindicated in systemic fungal infections, except when administered as an intra-articular injection for localized joint conditions (see **WARNINGS: Infections, Fungal Infections**).

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

This product contains benzyl alcohol, which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol in medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS: Pediatric Use**).

Multidose use of DEPO-MEDROL Sterile Aqueous Suspension from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. Particular care, such as use of disposable sterile syringes and needles, is necessary.

Injection of DEPO-MEDROL may result in dermal and/or subdermal changes, forming depressions in the skin at the injection site.

In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intra-articular and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

It is critical that, during administration of DEPO-MEDROL, appropriate technique be used and care taken to ensure proper placement of drug.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, or after the stressful situation (see **ADVERSE REACTIONS**).

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including DEPO-MEDROL, should not be used for the treatment of traumatic brain injury.

Cardio-renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between the use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced

secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Infections

General

Persons who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may mask some signs of current infection. Do not use intra-articularly, intrabursally, or for intratendinous administration for local effect in the presence of acute local infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**, *Amphotericin B injection and potassium-depleting agents*).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary, as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccinations

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., for Addison's disease).

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

When multidose vials are used, special care to prevent contamination of the contents is essential. A povidone-iodine solution or similar product is recommended to cleanse the vial top prior to aspiration of contents. (See

WARNINGS.)

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the outside of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Parenteral Administration

Intra-articular injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid is necessary to exclude a septic process.

A marked increase in pain associated by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Neuro-psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

Information for the Patient

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see **PRECAUTIONS: Drug Interactions, Hepatic Enzyme Inhibitors**).

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of oral corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs which induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin): Drugs which inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole: Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with concurrent use of corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin Tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or attenuated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS: Infections, Vaccinations**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis. Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

This product contains benzyl alcohol as a preservative.

Benzyl alcohol can cross the placenta. See **PRECAUTIONS: Pediatric use**.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to continue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product ordinarily delivers amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephritic syndrome (patients >2 years of age) and aggressive lymphomas and leukemias (patients >1 month of age). Other

indications for pediatric use of corticosteroids (e.g., severe asthma and wheezing) are based on adequate and well-controlled clinical trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported with DEPO-MEDROL or other corticosteroids:

Allergic reactions: Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible subsequent perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.

Ophthalmic: Exophthalmoses, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see **WARNINGS**), malaise, moon face, weight gain.

The following adverse reactions have been reported with the following routes of administration:

Intrathecal/Epidural: Arachnoiditis, bowel/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizures, sensory disturbances.

Intranasal: Allergic reactions, rhinitis, temporary/permanent visual impairment including blindness.

Ophthalmic: Increased intraocular pressure, infection, ocular and periocular inflammation including allergic reactions, residue or slough at injection site, temporary/permanent visual impairment including blindness.

Miscellaneous injection sites (scalp, tonsillar fauces, sphenopalatine ganglion): Blindness.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see **WARNINGS** and **PRECAUTIONS: Pediatric Use**)

Because of possible physical incompatibilities, DEPO-MEDROL Sterile Aqueous Suspension should not be diluted or mixed with other solutions.

The initial dosage of parenterally administered DEPO-MEDROL will vary from 4 to 120 mg, depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

It Should Be Emphasized that Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation, it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

A. Administration for Local Effect

Therapy with DEPO-MEDROL does not obviate the need for the conventional measures usually employed. Although this method of treatment will ameliorate symptoms, it is in no sense a cure and the hormone has no effect on the cause of the inflammation.

1. Rheumatoid Arthritis and Osteoarthritis. The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, injections may be repeated at intervals ranging from one to five or more weeks, depending upon the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide:

<i>Size of Joint</i>	<i>Examples</i>	<i>Range of Dosage</i>
Large	Knees	20 to 80 mg
	Ankles	
	Shoulders	
Medium	Elbows	10 to 40 mg
	Wrists	
Small	Metacarpophalangeal	4 to 10 mg
	Interphalangeal	
	Sternoclavicular	
	Acromioclavicular	

Procedure: It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect, it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the joint space has been entered by the needle. *The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves.* With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of DEPO-MEDROL. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing.

Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal, and hip joints. Since difficulty is not infrequently encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the

result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile.

If a local anesthetic is used prior to injection of DEPO-MEDROL, the anesthetic package insert should be read carefully and all the precautions observed.

2. Bursitis. The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 percent procaine hydrochloride solution. A 20 to 24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

3. Miscellaneous: Ganglion, Tendinitis, Epicondylitis. In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken following application of a suitable antiseptic to the overlying skin to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst. In many cases, a single injection causes a marked decrease in the size of the cystic tumor and may effect disappearance. The usual sterile precautions should be observed, of course, with each injection.

The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4 to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

4. Injections for Local Effect in Dermatologic Conditions. Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg of the suspension is injected into the lesion. It may be necessary to distribute doses ranging from 20 to 40 mg by repeated local injections in the case of large lesions. Care should be taken to avoid injection of sufficient material to cause blanching since this may be followed by a small slough. One to four injections are usually employed, the intervals between injections varying with the type of lesion being treated and the duration of improvement produced by the initial injection.

When multidose vials are used, special care to prevent contamination of the contents is essential. (See WARNINGS.)

B. Administration for Systemic Effect

The intramuscular dosage will vary with the condition being treated. When employed as a temporary substitute for oral therapy, a single injection during each

24-hour period of a dose of the suspension equal to the total daily oral dose of MEDROL[®] Tablets (methylprednisolone tablets, USP) is usually sufficient. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a single intramuscular injection.

In pediatric patients, the initial dose of methylprednisolone may vary depending upon the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day. Dosage must be individualized according to the severity of the disease and response of the patient.

In patients with the **adrenogenital syndrome**, a single intramuscular injection of 40 mg every two weeks may be adequate. For maintenance of patients with **rheumatoid arthritis**, the weekly intramuscular dose will vary from 40 to 120 mg. The usual dosage for patients with **dermatologic lesions** benefited by systemic corticoid therapy is 40 to 120 mg of methylprednisolone acetate administered intramuscularly at weekly intervals for one to four weeks. In acute severe dermatitis due to poison ivy, relief may result within 8 to 12 hours following intramuscular administration of a single dose of 80 to 120 mg. In chronic contact dermatitis, repeated injections at 5 to 10 day intervals may be necessary. In seborrheic dermatitis, a weekly dose of 80 mg may be adequate to control the condition.

Following intramuscular administration of 80 to 120 mg to asthmatic patients, relief may result within 6 to 48 hours and persist for several days to two weeks. Similarly, in patients with allergic rhinitis (hay fever), an intramuscular dose of 80 to 120 mg may be followed by relief of coryzal symptoms within six hours persisting for several days to three weeks.

If signs of stress are associated with the condition being treated, the dosage of the suspension should be increased. If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate is indicated.

In treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of methylprednisolone for a week followed by 64 mg every other day for 1 month have been shown to be effective.

For the purpose of comparison, the following is the equivalent milligram dose of the various glucocorticoids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

HOW SUPPLIED

DEPO-MEDROL Sterile Aqueous Suspension is available in the following strengths and package sizes:

20 mg per mL

5 mL multidose vials	NDC 0009-0274-01
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40 mg per mL

5 mL multidose vials	NDC 0009-0280-02
25 x 5 mL multidose vials	NDC 0009-0280-51
10 mL multidose vials	NDC 0009-0280-03
25 x 10 mL multidose vials	NDC 0009-0280-52

80 mg per mL

5 mL multidose vials	NDC 0009-0306-02
25 x 5 mL multidose vials	NDC 0009-0306-12

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

 **Injectables**
Distributed by
Pharmacia & Upjohn Co
Division of Pfizer Inc
New York, NY 10017

LAB-0159-8.4
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DEPO-MEDROL®

(methylprednisolone acetate injectable suspension, USP)

Single-Dose Vial

Not For Intravenous Use

DESCRIPTION

DEPO-MEDROL is an anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue or intralesional injection. It is available as single-dose vials in two strengths: 40 mg/mL, 80 mg/mL.

Each mL of these preparations contains:

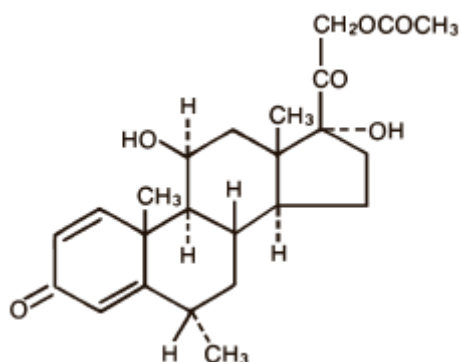
Methylprednisolone acetate	40 mg80 mg
Polyethylene glycol 3350	29 mg28 mg
Myristyl-gamma-picolinium chloride.....	0.195 mg0.189 mg

Sodium Chloride was added to adjust tonicity.

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

The pH of the finished product remains within the USP specified range (e.g., 3.0 to 7.0.)

The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-, (6 α ,11 β)- and the molecular weight is 416.51. The structural formula is represented below:



DEPO-MEDROL Sterile Aqueous Suspension contains methylprednisolone acetate which is the 6-methyl derivative of prednisolone. Methylprednisolone acetate is a white or practically white, odorless, crystalline powder which melts at about 215° with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, alcohol, chloroform, and methanol, and slightly soluble in ether. It is practically insoluble in water.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt retaining properties, are used in replacement therapy in adrenocortical deficiency states. Their synthetic analogs are used primarily for their anti-inflammatory effects in disorders of many organ systems.

INDICATIONS AND USAGE

A. For Intramuscular Administration

When oral therapy is not feasible and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the intramuscular use of DEPO-MEDROL Sterile Aqueous Suspension is indicated as follows:

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, seasonal or perennial allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic Diseases: Bullous dermatitis herpetiformis, exfoliative dermatitis, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsupportive thyroiditis.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis.

Hematologic Disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond Blackfan anemia), pure red cell aplasia, select cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Neoplastic Diseases: For palliative management of: leukemias and lymphomas.

Nervous System: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor or craniotomy.

Ophthalmic Diseases: Sympathetic ophthalmia, temporal arteritis, uveitis, ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal Diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, or that due to lupus erythematosus.

Respiratory Diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic Disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

**B. For Intra-articular Or Soft Tissue Administration
(See WARNINGS)**

DEPO-MEDROL is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

C. For Intralesional Administration

DEPO-MEDROL is indicated for intralesional use in alopecia areata, discoid lupus erythematosus; keloids, localized hypertrophic, infiltrated inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis) and psoriatic plaques; necrobiosis lipoidica diabetorum.

DEPO-MEDROL also may be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

DEPO-MEDROL is contraindicated in patients with known hypersensitivity to the product and its constituents.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

DEPO-MEDROL is contraindicated for intrathecal administration. This formulation of methylprednisolone acetate has been associated with reports of severe medical events when administered by this route.

DEPO-MEDROL is contraindicated in systemic fungal infections, except when administered as an intra-articular injection for localized joint conditions (see **WARNINGS: Infections, *Fungal Infections***).

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

This product is not suitable for multi-dose use. Following administration of the desired dose, any remaining suspension should be discarded.

Injection of DEPO-MEDROL may result in dermal and/or subdermal changes forming depressions in the skin at the injection site.

In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intra-articular and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

It is critical that, during administration of DEPO-MEDROL, appropriate technique be used and care taken to ensure proper placement of drug.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including DEPO-MEDROL, should not be used for the treatment of traumatic brain injury.

Cardio-renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with synthetic derivatives when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Hypothalamic-pituitary adrenal (HPA) axis suppression. Cushing's syndrome, and Hyperglycemia: Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Infections

General

Persons who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Do not use intra-articularly, intrabursally, or for intratendinous administration for local effect in the presence of an acute infection. Corticosteroids may mask some signs of infection and new infections may appear during their use.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug interactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**, *Amphotericin B injection and potassium-depleting agents*).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary, as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccinations

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.

Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g., for Addison's disease).

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated (see the respective package inserts for

complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents should be considered.

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

This product, like many other corticosteroids, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticosteroids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Karposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Parenteral Administration

Intra-articularly injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to an inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Neuro-psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see **DOSAGE AND ADMINISTRATION**).

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g.,

myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued long-term, intraocular pressure should be monitored.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

Information for the Patient

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop a fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see **PRECAUTIONS: Drug Interactions, Hepatic Enzyme Inhibitors**).

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentration, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of oral corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs which induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin): Drugs which inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole: Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody

response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS: Infections, Vaccinations**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephritic syndrome (patients >2 years of age) and aggressive lymphomas and leukemias (patients >1 month of age). Other indications for pediatric use of corticosteroids (e.g., severe asthma and wheezing) are based on adequate and well-controlled clinical trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and

osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported with DEPO-MEDROL or other corticosteroids:

Allergic reactions: Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary

unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible subsequent perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intra-lesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.

Ophthalmic: Exophthalmoses, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see **WARNINGS**), malaise, moon face, weight gain.

The following adverse reactions have been reported with the following routes of administration:

Intrathecal/Epidural: Arachnoiditis, bowel/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizures, sensory disturbances.

Intranasal: Allergic reactions, rhinitis, temporary/permanent visual impairment including blindness.

Ophthalmic: Increased intraocular pressure, infection, ocular and periocular inflammation including allergic reactions, residue or slough at injection site, temporary/permanent visual impairment including blindness.

Miscellaneous injection sites (scalp, tonsillar fauces, sphenopalatine ganglion): blindness.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

Because of possible physical incompatibilities, DEPO-MEDROL Sterile Aqueous Suspension should not be diluted or mixed with other solutions.

The initial dosage of parenterally administered DEPO-MEDROL will vary from 4 to 120 mg, depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

It Should Be Emphasized that Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation, it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

A. Administration for Local Effect

Therapy with DEPO-MEDROL does not obviate the need for the conventional measures usually employed. Although this method of treatment will ameliorate symptoms, it is in no sense a cure and the hormone has no effect on the cause of the inflammation.

1. Rheumatoid Arthritis and Osteoarthritis. The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, injections may be repeated at intervals ranging from one to five or more weeks, depending upon the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide:

<i>Size of Joint</i>	<i>Examples</i>	<i>Range of Dosage</i>
Large	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	10 to 40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

Procedure: It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect, it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the joint space has been entered by the needle. *The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves.* With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the desired amount of DEPO-MEDROL. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of the synovial fluid and the suspension. The site is covered with a small sterile dressing.

Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal, and hip joints. Since difficulty is not infrequently encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile.

If a local anesthetic is used prior to injection of DEPO-MEDROL, the anesthetic package insert should be read carefully and all the precautions observed.

2. Bursitis. The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 percent procaine hydrochloride solution. A 20 to 24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a

small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

3. Miscellaneous: Ganglion, Tendinitis, Epicondylitis. In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken following application of a suitable antiseptic to the overlying skin to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst. In many cases, a single injection causes a marked decrease in the size of the cystic tumor and may effect disappearance. The usual sterile precautions should be observed, of course, with each injection.

The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4 to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

4. Injections for Local Effect in Dermatologic Conditions. Following cleansing with an appropriate antiseptic such as 70% alcohol, 20 to 60 mg of the suspension is injected into the lesion. It may be necessary to distribute doses ranging from 20 to 40 mg by repeated local injections in the case of large lesions. Care should be taken to avoid injection of sufficient material to cause blanching since this may be followed by a small slough. One to four injections are usually employed, the intervals between injections varying with the type of lesion being treated and the duration of improvement produced by the initial injection.

B. Administration for Systemic Effect.

The intramuscular dosage will vary with the condition being treated. When employed as a temporary substitute for oral therapy, a single injection during each 24-hour period of a dose of the suspension equal to the total daily oral dose of MEDROL[®] Tablets (methylprednisolone tablets, USP) is usually sufficient. When a prolonged effect is desired, the weekly dose may be calculated by multiplying the daily oral dose by 7 and given as a single intramuscular injection.

In pediatric patients, the initial dose of methylprednisolone may vary depending on the specific disease entity being treated. Dosage must be individualized according to the severity of the disease and response of the patient. The recommended dosage may be reduced for pediatric patients, but dosage should be governed by the severity of the condition rather than by strict adherence to the ratio indicated by age or body weight.

In patients with the **adrenogenital syndrome**, a single intramuscular injection of 40 mg every two weeks may be adequate. For maintenance of patients with

rheumatoid arthritis, the weekly intramuscular dose will vary from 40 to 120 mg. The usual dosage for patients with **dermatologic lesions** benefited by systemic corticoid therapy is 40 to 120 mg of methylprednisolone acetate administered intramuscularly at weekly intervals for one to four weeks. In acute severe dermatitis due to poison ivy, relief may result within 8 to 12 hours following intramuscular administration of a single dose of 80 to 120 mg. In chronic contact dermatitis, repeated injections at 5 to 10 day intervals may be necessary. In seborrheic dermatitis, a weekly dose of 80 mg may be adequate to control the condition.

Following intramuscular administration of 80 to 120 mg to asthmatic patients, relief may result within 6 to 48 hours and persist for several days to two weeks. Similarly, in patients with allergic rhinitis (hay fever), an intramuscular dose of 80 to 120 mg may be followed by relief of coryzal symptoms within six hours persisting for several days to three weeks.

If signs of stress are associated with the condition being treated, the dosage of the suspension should be increased. If a rapid hormonal effect of maximum intensity is required, the intravenous administration of highly soluble methylprednisolone sodium succinate is indicated.

In treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of methylprednisolone for a week followed by 64 mg every other day for 1 month have been shown to be effective.

For the purpose of comparison, the following is the equivalent milligram dose of the various glucocorticoids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

HOW SUPPLIED

DEPO-MEDROL Sterile Aqueous Suspension is available as single-dose vials in the following strengths and package sizes:

40 mg per mL

1 mL vials NDC 0009-3073-01
25 x 1 mL vials NDC 0009-3073-03

80 mg per mL

1 mL vials NDC 0009-3475-01
25 x 1 mL vials NDC 0009-3475-03

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].



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SOLU-MEDROL[®] (methylprednisolone sodium succinate for injection, USP)

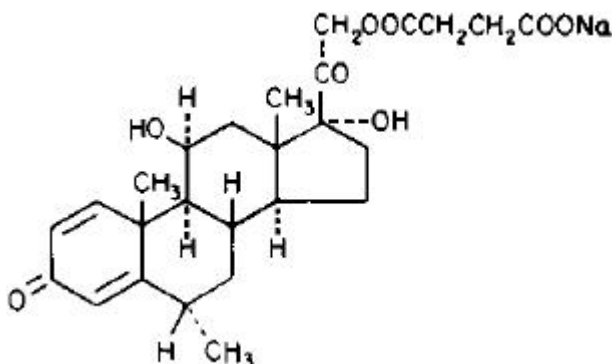
The formulations containing benzyl alcohol should not be used in neonates.

For Intravenous or Intramuscular Administration

DESCRIPTION

SOLU-MEDROL Sterile Powder is an anti-inflammatory glucocorticoid, which contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate, USP, is the sodium succinate ester of methylprednisolone, and it occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

The chemical name for methylprednisolone sodium succinate is pregna-1,4-diene-3,20-dione,21-(3-carboxy-1-oxopropoxy)-11,17-dihydroxy-6-methyl-monosodium salt, (6 α , 11 β), and the molecular weight is 496.53. The structural formula is represented below:



Methylprednisolone sodium succinate is soluble in water; it may be administered in a small volume of diluent and is well suited for intravenous use in situations where high blood levels of methylprednisolone are required rapidly.

SOLU-MEDROL is available in preservative and preservative-free formulations:

Preservative-free Formulations
40 mg Act-O-Vial System (Single-Use Vial) —Each mL (when mixed) contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; 17.46 mg dibasic sodium phosphate dried; and 25 mg lactose hydrous.
125 mg Act-O-Vial System (Single-Use Vial) —Each 2 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; and 17.4 mg dibasic sodium phosphate dried.

500 mg Act-O-Vial System (Single-Use Vial)—Each 4 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; and 69.6 mg dibasic sodium phosphate dried.

1 gram Act-O-Vial System (Single-Use Vial)—Each 8 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 1 gram methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; and 139.2 mg dibasic sodium phosphate dried.

Formulations preserved with Benzyl Alcohol

40 mg Act-O-Vial System (Single-Use Vial)—Each mL (when mixed) contains methylprednisolone sodium succinate equivalent to 40 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; 17.46 mg dibasic sodium phosphate dried; 25 mg lactose hydrous; 8.8 mg benzyl alcohol added as preservative.

125 mg Act-O-Vial System (Single-Use Vial)—Each 2 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 125 mg methylprednisolone; also 1.6 mg monobasic sodium phosphate anhydrous; 17.4 mg dibasic sodium phosphate dried; 17.6 mg benzyl alcohol added as preservative.

500 mg Act-O-Vial System (Single-Use Vial)—Each 4 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; 69.6 mg dibasic sodium phosphate dried; 33.7 mg benzyl alcohol added as preservative.

1 gram Act-O-Vial System (Single-Use Vial)—Each 8 mL (when mixed) contains methylprednisolone sodium succinate equivalent to 1 gram methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried; 66.8 mg benzyl alcohol added as preservative.

500 mg Vial—Each 8 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; 69.6 mg dibasic sodium phosphate dried.
This package does not contain diluent. Recommended diluent (Bacteriostatic water) contains benzyl alcohol as a preservative.

1 gram Vial—Each 16 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 1 gram methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried.
This package does not contain diluent. Recommended diluent (Bacteriostatic water) contains benzyl alcohol as a preservative.

2 gram Vial with Diluent—Each 30.6 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 2 grams methylprednisolone; also 25.6 mg monobasic sodium phosphate anhydrous; 278 mg dibasic sodium phosphate dried; 273 mg benzyl alcohol added as preservative.
The packaged diluent (Bacteriostatic Water for Injection) contains benzyl alcohol as a preservative.

IMPORTANT — Use only the accompanying diluent

or Bacteriostatic Water For Injection with
Benzyl Alcohol when reconstituting SOLU-MEDROL.
Use within 48 hours after mixing.

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8 and the tonicities are, for the 40 mg per mL solution, 0.50 osmolar; for the 125 mg per 2 mL solution, 0.40 osmolar; for the 1 gram per 8 mL solution, 0.44 osmolar; for the 2 gram per 30.6 mL solutions, 0.42 osmolar. (Isotonic saline = 0.28 osmolar.)

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

Methylprednisolone is a potent anti-inflammatory steroid with greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. Following the intravenous injection of methylprednisolone sodium succinate, demonstrable effects are evident within one hour and persist for a variable period. Excretion of the administered dose is nearly complete within 12 hours. Thus, if constantly high blood levels are required, injections should be made every 4 to 6 hours. This preparation is also rapidly absorbed when administered intramuscularly and is excreted in a pattern similar to that observed after intravenous injection.

INDICATIONS AND USAGE

When oral therapy is not feasible, and the strength, dosage form, and route of administration of the drug reasonably lend the preparation to the treatment of the condition, the **intravenous or intramuscular use** of SOLU-MEDROL Sterile Powder is indicated as follows:

Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis (systemic therapy) and ulcerative colitis.

Hematologic disorders: Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults (intravenous administration only; intramuscular administration is contraindicated), pure red cell aplasia, selected cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy.

Neoplastic diseases: For the palliative management of leukemias and lymphomas.

Nervous System: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, or craniotomy.

Ophthalmic diseases: Sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, temporal arteritis, polymyositis, and systemic lupus erythematosus.

CONTRAINDICATIONS

SOLU-MEDROL Sterile Powder is contraindicated:

- in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.
- for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

Additional contraindication for the use of SOLU-MEDROL Sterile Powder preserved with benzyl alcohol:

Formulations preserved with benzyl alcohol are contraindicated for use in premature infants. (See **WARNINGS** and **PRECAUTIONS, Pediatric Use**.)

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

Formulations with preservative (see DESCRIPTION) contain benzyl alcohol, which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS, Pediatric Use**).

Injection of SOLU-MEDROL may result in dermal and/or subdermal changes forming depressions in the skin at the injection site. In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy who are subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including SOLU-MEDROL, should not be used for the treatment of traumatic brain injury.

Cardio-renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between the use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection. Do not use intra-articularly, intrabursally or for intratendinous administration for local effect in the presence of acute local infection.

A study has failed to establish the efficacy of methylprednisolone sodium succinate in the treatment of sepsis syndrome and septic shock. The study also suggests that treatment of these conditions with methylprednisolone sodium succinate may increase the risk of mortality in certain patients (i.e., patients with elevated serum creatinine levels or patients who develop secondary infections after methylprednisolone sodium succinate).

Fungal infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **CONTRAINDICATIONS** and **PRECAUTIONS, Drug Interactions, Amphotericin B injection and potassium-depleting agents**).

Special pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines can not be predicted.

Immunization procedures may be undertaken in patients receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Viral infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Reports of severe medical events have been associated with the intrathecal route of administration (see **ADVERSE REACTIONS**, *Gastrointestinal* and *Neurologic/Psychiatric*).

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation. Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Local injection of a steroid into a previously infected site is not usually recommended.

Neurologic-psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies

do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see **Drug Interactions**, *Hepatic Enzyme Inhibitors*).

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible,

anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin): Drugs which induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin): Drugs which inhibit cytochrome P450 3A4 have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole: Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory agents (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS, Infections, Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy: Teratogenic effects: Pregnancy Category C.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

This product contains benzyl alcohol as a preservative.

Benzyl alcohol can cross the placenta. See **PRECAUTIONS: Pediatric use**.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to continue nursing, or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Some formulations of this product contain benzyl alcohol as a preservative (see **DESCRIPTION**). Carefully examine vials to determine formulation that is being used.

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product ordinarily delivers amounts of benzyl alcohol that are substantially lower than those reported in association with the

“gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported with SOLU-MEDROL or other corticosteroids:

Allergic reactions: Allergic or hypersensitivity reactions, anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, burning or tingling (especially in the perineal area after intravenous injection), cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see **WARNINGS, Neurologic**).

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see **WARNINGS**), malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

NOTE: Some of the SOLU-MEDROL formulations contain benzyl alcohol (see DESCRIPTION, WARNINGS and PRECAUTIONS, Pediatric Use)

Because of possible physical incompatibilities, SOLU-MEDROL should not be diluted or mixed with other solutions.

Use only the accompanying diluent or Bacteriostatic Water For Injection with Benzyl Alcohol when reconstituting SOLU-MEDROL (see DESCRIPTION). Use within 48 hours after mixing.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

This preparation may be administered by intravenous injection, by intravenous infusion, or by intramuscular injection, the preferred method for initial emergency use being intravenous injection. Following the initial emergency period, consideration should be given to employing a longer acting injectable preparation or an oral preparation.

There are reports of cardiac arrhythmias and/or cardiac arrest following the rapid administration of large IV doses of SOLU-MEDROL (**greater than 0.5 gram administered over a period of less than 10 minutes**). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion. When high dose therapy is desired, the recommended dose of SOLU-MEDROL Sterile Powder is 30 mg/kg **administered intravenously over at least 30 minutes**. This dose may be repeated every 4 to 6 hours for 48 hours.

In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized; usually not beyond 48 to 72 hours.

In other indications, initial dosage will vary from 10 to 40 mg of methylprednisolone depending on the specific disease entity being treated. However, in certain

overwhelming, acute, life-threatening situations, administrations in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages. *It Should Be Emphasized that Dosage Requirements are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient.* After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation, it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

SOLU-MEDROL may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution as directed. The desired dose may be administered intravenously over a period of several minutes. If desired, the medication may be administered in diluted solutions by adding Water for Injection or other suitable diluent (see below) to the **Act-O-Vial** and withdrawing the indicated dose.

To prepare solutions for intravenous infusion, first prepare the solution for injection as directed. This solution may then be added to indicated amounts of 5% dextrose in water, isotonic saline solution, or 5% dextrose in isotonic saline solution.

In pediatric patients, the initial dose of methylprednisolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in three or four divided doses (3.2 to 48 mg/m²bsa/day).

The National Heart, Lung, and Blood Institute (NHLBI) recommended dosing for systemic *prednisone*, *prednisolone*, or *methylprednisolone* in pediatric patients whose asthma is uncontrolled by inhaled corticosteroids and long-acting bronchodilators is 1-2 mg/kg/day in single or divided doses. It is further recommended that short course, or "burst" therapy, be continued until the patient achieves a peak expiratory flow rate of 80% of his or her personal best or until symptoms resolve. This usually requires 3 to 10 days of treatment, although it can take longer. There is no evidence that tapering the dose after improvement will prevent a relapse.

Dosage may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg per kg every 24 hours.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a

chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

In treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of methylprednisolone for a week followed by 64 mg every other day for 1 month have been shown to be effective (see **PRECAUTIONS, Neurologic-psychiatric**).

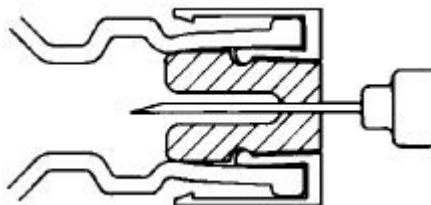
For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

DIRECTIONS FOR USING THE ACT-O-VIAL SYSTEM

1. Press down on plastic activator to force diluent into the lower compartment.
2. Gently agitate to effect solution.
3. Remove plastic tab covering center of stopper.
4. Sterilize top of stopper with a suitable germicide.
5. Insert needle **squarely through center** of stopper until tip is just visible. Invert vial and withdraw dose.



STORAGE CONDITIONS

Protect from light.

Store unconstituted product at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Store solution at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Use solution within 48 hours after mixing.

HOW SUPPLIED

SOLU-MEDROL Sterile Powder preserved with benzyl alcohol is available in the following packages:

500 mg (Multi-Dose Vial)

8 mL NDC 0009-0758-01

1 gram (Multi-Dose Vial)

16 mL NDC 0009-0698-01

2 gram Vial with Diluent

NDC 0009-0796-01

SOLU-MEDROL Sterile Powder **preservative-free** is available in the following packages:

40 mg Act-O-Vial System (Single-Use Vial)

25 x1 mL NDC 0009-0039-28

1 gram Act-O-Vial System (Single-Use Vial)

8 mL NDC 0009-0018-20

125 mg Act-O-Vial System (Single-Use Vial)

25 x 2 mL NDC 0009-0047-22

500 mg Act-O-Vial System (Single-Use Vial)

4 mL NDC 0009-0003-02



LAB-0161-7.3

Revised July 2014

Aristocort®
(Triamcinolone Diacetate, USP) Injectable Suspension

25 mg/mL PARENTERAL

NOT FOR USE IN NEONATES

NOT FOR INTRAVENOUS USE

CONTAINS BENZYL ALCOHOL

DESCRIPTION

Aristocort® is a sterile suspension of 25 mg/mL of triamcinolone diacetate (micronized) suspended in a vehicle consisting of:

Polysorbate 80	0.20%
Polyethylene Glycol	3%
Sodium Chloride	0.85%
Benzyl Alcohol	0.90%
Water for Injection q.s.	100%

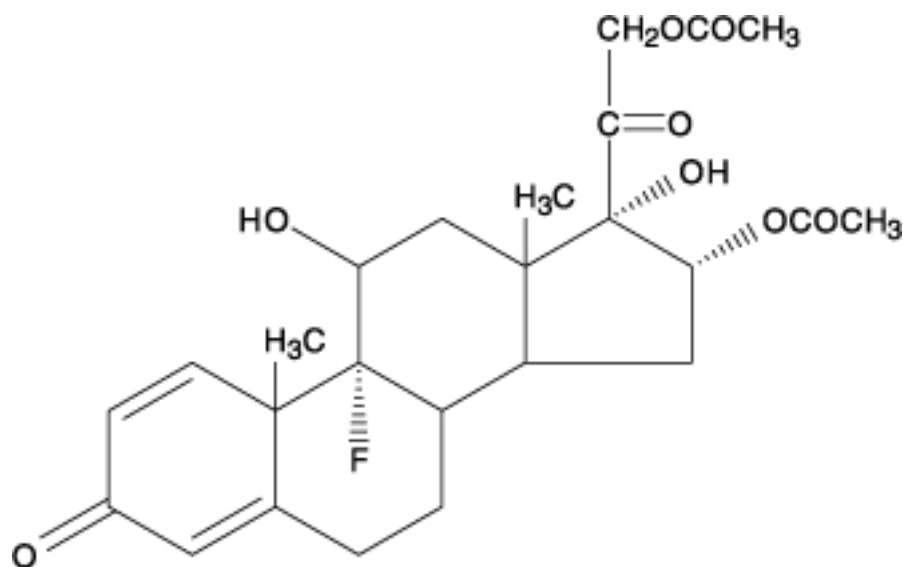
Hydrochloric acid and/or sodium hydroxide may be used during manufacture to adjust pH of suspension to approximately 6.

Triamcinolone diacetate is practically insoluble in water; soluble in chloroform; sparingly soluble in alcohol and in methanol; and slightly soluble in ether. This preparation is suitable for parenteral administration through a 23-gauge needle (or larger), but NOT suitable for intravenous use. It may be administered by the intramuscular, intra-articular, or intrasynovial routes, depending upon the situation.

Irreversible clumping occurs when this product is frozen.

Chemically triamcinolone diacetate is 9-fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,21-diacetate.

The molecular weight is 478.51. Its structural formula is:



Triamcinolone diacetate occurs as a white to off-white, microcrystalline powder.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily adsorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Triamcinolone diacetate is essentially devoid of mineralocorticoid activity when administered in therapeutic doses, causing little or no sodium retention with potassium excretion minimal or absent.

INDICATIONS AND USAGE

Where oral therapy is not feasible, Aristocort® (triamcinolone diacetate injectable suspension), 25 mg/mL, is indicated for intramuscular use as follows:

Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic Diseases

Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal Disease

To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic Disorders

Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

Miscellaneous

Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic Diseases

For palliative management of leukemias and lymphomas.

Nervous System

Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, or craniotomy.

Ophthalmic Diseases

Sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal Diseases

To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory Diseases

Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic

arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

For Intra-Articular or Soft Tissue Administration

The intra-articular or soft tissue administration of Aristocort® is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

For Intralesional Administration

The intralesional administration of Aristocort® is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques; necrobiosis lipoidica diabetorum.

It may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Aristocort® is contraindicated in patients who are hypersensitive to any components of this product.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

Aristocort® is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

Aristocort is contraindicated for use in premature infants because the formulation contains benzyl alcohol (see [WARNINGS](#) and [PRECAUTIONS: Pediatric Use](#)).

Aristocort is contraindicated in systemic fungal infections, except when administered as an intra-articular injection for localized joint conditions (see [WARNINGS: Infections:Fungal Infections](#)).

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see [PRECAUTIONS: Pediatric Use](#)).

It is critical that, during administration of Aristocort®, appropriate technique be used and care taken to assure proper placement of drug.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see [ADVERSE REACTIONS](#)).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including Aristocort®, should not be used for the treatment of traumatic brain injury.

Cardio-renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant uses of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see [PRECAUTIONS: Drug Interactions: Amphotericin B Injection and Potassium-Depleting Agents](#)).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Toxoplasma.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines can not be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Reports of severe adverse reactions have been associated with the intrathecal route of administration (see [ADVERSE REACTIONS: Neurologic/Psychiatric](#)).

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Atrophy at the site of injection has been reported.

Cardio-renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcer, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to increased metabolism of corticosteroids in patients with cirrhosis.

Intra-Articular and Soft Tissue Administration

Intra-articularly injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Neurologic/Psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See [DOSAGE AND ADMINISTRATION](#).)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in

patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide

Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B Injection and Potassium-Depleting Agents

When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics

Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see [Drug Interactions: Hepatic Enzyme Inhibitors](#)).

Anticholinesterases

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, Oral

Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular Drugs

Serum concentrations of isoniazid may be decreased.

Cholestyramine

Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis Glycosides

Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including Oral Contraceptives

Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., Barbiturates, Phenytoin, Carbamazepine, Rifampin)

Drugs which induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin)

Drugs which inhibit cytochrome P450 3A4 enzyme activity have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole

Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal Anti-Inflammatory Agents (NSAIDs)

Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin Tests

Corticosteroids may suppress reactions to skin tests.

Vaccines

Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see [WARNINGS: Vaccination](#)).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to continue nursing, or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome,” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological

deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome,” the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see [ADVERSE REACTIONS](#)). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

(listed alphabetically, under each subsection)

Allergic Reactions

Allergic or hypersensitivity reactions, anaphylactoid reactions, anaphylaxis, angioedema.

Cardiovascular

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see [WARNINGS](#)), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic

Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine

Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal

Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic

Negative nitrogen balance due to protein catabolism.

Musculoskeletal

Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intra-lesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric

Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see [WARNINGS: Neurologic](#)).

Ophthalmic

Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other

Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see [WARNINGS](#)), malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see [WARNINGS](#) and [PRECAUTIONS: Pediatric Use](#))

Because of possible physical incompatibilities, Aristocort® Sterile Aqueous Suspension should not be diluted or mixed with other solutions.

General

The initial intramuscular dosage of triamcinolone diacetate injectable suspension may vary from 3 to 48 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

It Should be Emphasized that Dosage Requirements are Variable and Must be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of triamcinolone for a week followed by 64 mg every other day for one month are recommended (see [PRECAUTIONS: Neurologic/Psychiatric](#)).

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in three or four divided doses (3.2 to 48 mg/m² bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

<i>Betamethasone, 0.75</i>	<i>Methylprednisolone, 4</i>
<i>Cortisone, 25</i>	<i>Paramethasone, 2</i>
<i>Dexamethasone, 0.75</i>	<i>Prednisolone, 5</i>
<i>Hydrocortisone, 20</i>	<i>Triamcinolone, 4</i>

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

Specific

Aristocort® Parenteral is triamcinolone diacetate injectable suspension (25 mg/mL) suspended in a suitable vehicle. The full-strength suspension may be employed. Topical ethyl chloride spray may be used locally prior to injection.

Since this product has been designed for ease of administration, a small bore needle (not smaller than 23 gauge) may be used.

Intramuscular

Although Aristocort® Parenteral may be administered intramuscularly for initial therapy, most physicians prefer to adjust the dose orally until adequate control is attained. Intramuscular administration provides a sustained or depot action which can be used to supplement or replace initial oral therapy. With intramuscular therapy, greater supervision of the amount of steroid used is made possible in the patient who is inconsistent in following an oral dosage schedule. In maintenance therapy, the patient-to-patient response is not uniform and, therefore, the dose must be individualized for optimal control.

The average dose is 25mg (1 mL) administered intramuscularly once a week for conditions in which anti-inflammatory action is desired.

In general, a single parenteral dose 4 to 7 times the oral daily dose may be expected to control the patient from 4 to 7 days up to 3 to 4 weeks. Dosage should be adjusted to the point where adequate but not necessarily complete relief of symptoms is obtained.

Intra-Articular and Intrasynovial

The usual dose varies from 5 to 40 mg. The average for the knee, for example, is 25 mg. The duration of effect varies from one week to 2 months. However, acutely inflamed joints may require more frequent injections.

A lesser initial dosage range of triamcinolone diacetate injectable suspension may produce the desired effect when the drug is administered to provide a localized concentration. The site of the

injection and the volume of the injection should be carefully considered when triamcinolone diacetate is administered for this purpose.

A specific dose depends largely on the size of the joint.

Strict surgical asepsis is mandatory. The physician should be familiar with anatomical relationships as described in standard textbooks. Aristocort® Parenteral may be used in any accessible joint except the intervertebrals. In general, intrasynovial therapy is suggested under the following circumstances:

1. When systemic steroid therapy is contraindicated because of side effects such as peptic ulcer.
2. When it is desirable to secure relief in one or two specific joints.
3. When good systemic maintenance fails to control flare-ups in a few joints, and it is desirable to secure relief without increasing oral therapy.

Such treatment should not be considered to constitute a cure, for although this method will ameliorate the joint symptoms, it does not preclude the need for the conventional measures usually employed.

It is suggested that infiltration of the soft tissue by local anesthetic precede intra-articular injection. A 24-gauge or larger needle on a dry syringe may be inserted into the joint and excess fluid aspirated. For the first few hours following injection, there may be local discomfort in the joint but this is usually followed rapidly by effective relief of pain and improvement in local function.

HOW SUPPLIED

Aristocort® (triamcinolone diacetate injectable suspension), 25 mg/mL, parenteral, Not For Intravenous Use, supplied as follows:

NDC 0781-3036-75 25 mg/mL (5 mL Fill in a 10 mL Vial), boxes of 1

Protect from light.

DO NOT FREEZE

SHAKE WELL

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Irreversible clumping occurs when product is frozen.

04-2014M

U100XXXX

Manufactured in Canada by

Sandoz Canada Inc. for

Sandoz Inc., Princeton, NJ 08540

Aristocort® Forte
(Triamcinolone Diacetate, USP) Injectable Suspension

40 mg/mL PARENTERAL

NOT FOR USE IN NEONATES

NOT FOR INTRAVENOUS USE

CONTAINS BENZYL ALCOHOL

DESCRIPTION

Aristocort® Forte is a sterile suspension of 40 mg/mL of triamcinolone diacetate (micronized) suspended in a vehicle consisting of:

Polysorbate 80	0.20%
Polyethylene Glycol	3%
Sodium Chloride	0.85%
Benzyl Alcohol	0.90%
Water for Injection q.s.	100%

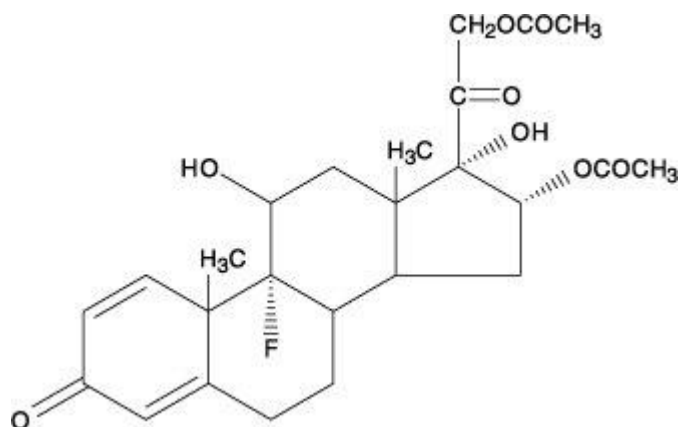
Hydrochloric acid and/or sodium hydroxide may be used during manufacture to adjust pH of suspension to approximately 6.

Triamcinolone diacetate is practically insoluble in water; soluble in chloroform; sparingly soluble in alcohol and in methanol; and slightly soluble in ether. This preparation is suitable for parenteral administration through a 23-gauge needle (or larger), but NOT suitable for intravenous use. It may be administered by the intramuscular, intra-articular, or intrasynovial routes, depending upon the situation.

Irreversible clumping occurs when this product is frozen.

Chemically triamcinolone diacetate is 9-fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione 16,21-diacetate.

The molecular weight is 478.51. Its structural formula is:



Triamcinolone diacetate occurs as a white to off-white, microcrystalline powder.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily adsorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Triamcinolone diacetate is essentially devoid of mineralocorticoid activity when administered in therapeutic doses, causing little or no sodium retention with potassium excretion minimal or absent.

INDICATIONS AND USAGE

Where oral therapy is not feasible, Aristocort® Forte (triamcinolone diacetate injectable suspension), 40 mg/mL, is indicated for intramuscular use as follows:

Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic Diseases

Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal Disease

To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic Disorders

Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

Miscellaneous

Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic Diseases

For palliative management of leukemias and lymphomas.

Nervous System

Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor, or craniotomy.

Ophthalmic Diseases

Sympathetic ophthalmia, uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal Diseases

To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory Diseases

Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

For Intra-Articular or Soft Tissue Administration

The intra-articular or soft tissue administration of Aristocort® Forte is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

For Intralesional Administration

The intralesional administration of Aristocort® Forte is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques; necrobiosis lipoidica diabetorum.

It may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Aristocort® Forte is contraindicated in patients who are hypersensitive to any components of this product.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

Aristocort® Forte is contraindicated for intrathecal administration. Reports of severe medical events have been associated with this route of administration.

Aristocort Forte is contraindicated for use in premature infants because the formulation contains benzyl alcohol (see [WARNINGS](#) and [PRECAUTIONS: Pediatric Use](#)).

Aristocort Forte is contraindicated in systemic fungal infections, except when administered as an intra-articular injection for localized joint conditions (see [WARNINGS: Infections: Fungal Infections](#)).

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see [PRECAUTIONS: Pediatric Use](#)).

It is critical that, during administration of Aristocort® Forte, appropriate technique be used and care taken to assure proper placement of drug.

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see [ADVERSE REACTIONS](#)).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including Aristocort®, should not be used for the treatment of traumatic brain injury.

Cardio-renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant uses of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see [**PRECAUTIONS: Drug Interactions: Amphotericin B Injection and Potassium-Depleting Agents**](#)).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines can not be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be

indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Reports of severe adverse reactions have been associated with the intrathecal route of administration (see [ADVERSE REACTIONS: Neurologic/Psychiatric](#)).

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Atrophy at the site of injection has been reported.

Cardio-renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since

mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcer, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to increased metabolism of corticosteroids in patients with cirrhosis.

Intra-Articular and Soft Tissue Administration

Intra-articularly injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Neurologic/Psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See [DOSAGE AND ADMINISTRATION](#).)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide

Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B Injection and Potassium-Depleting Agents

When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics

Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see [Drug Interactions: Hepatic Enzyme Inhibitors](#)).

Anticholinesterases

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, Oral

Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular Drugs

Serum concentrations of isoniazid may be decreased.

Cholestyramine

Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis Glycosides

Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including Oral Contraceptives

Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., Barbiturates, Phenytoin, Carbamazepine, Rifampin)

Drugs which induce cytochrome P450 3A4 enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Hepatic Enzyme Inhibitors (e.g., ketoconazole, macrolide antibiotics such as erythromycin and troleandomycin)

Drugs which inhibit cytochrome P450 3A4 enzyme activity have the potential to result in increased plasma concentrations of corticosteroids.

Ketoconazole

Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal Anti-Inflammatory Agents (NSAIDs)

Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin Tests

Corticosteroids may suppress reactions to skin tests.

Vaccines

Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see [WARNINGS: Vaccination](#)).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to continue nursing, or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome,” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome,” the minimum amount

of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see [ADVERSE REACTIONS](#)). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

(listed alphabetically, under each subsection)

Allergic Reactions

Allergic or hypersensitivity reactions, anaphylactoid reactions, anaphylaxis, angioedema.

Cardiovascular

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see [WARNINGS](#)), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic

Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine

Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal

Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic

Negative nitrogen balance due to protein catabolism.

Musculoskeletal

Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intra-lesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric

Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis,

meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see [WARNINGS: Neurologic](#)).

Ophthalmic

Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other

Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, injection site infections following non-sterile administration (see [WARNINGS](#)), malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see [WARNINGS](#) and [PRECAUTIONS: Pediatric Use](#))

Because of possible physical incompatibilities, Aristocort® Forte Sterile Aqueous Suspension should not be diluted or mixed with other solutions.

General

The initial intramuscular dosage of triamcinolone diacetate injectable suspension may vary from 3 to 48 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

It Should be Emphasized that Dosage Requirements are Variable and Must be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of triamcinolone for a week followed by 64 mg every other day for one month are recommended (see [PRECAUTIONS: Neurologic/Psychiatric](#)).

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in three or four divided doses (3.2 to 48 mg/m² bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

<i>Betamethasone, 0.75</i>	<i>Methylprednisolone, 4</i>
<i>Cortisone, 25</i>	<i>Paramethasone, 2</i>
<i>Dexamethasone, 0.75</i>	<i>Prednisolone, 5</i>
<i>Hydrocortisone, 20</i>	<i>Triamcinolone, 4</i>

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

Specific

Aristocort® Forte Parenteral is triamcinolone diacetate injectable suspension (40 mg/mL) suspended in a suitable vehicle. The full-strength suspension may be employed. Topical ethyl chloride spray may be used locally prior to injection.

Since this product has been designed for ease of administration, a small bore needle (not smaller than 23 gauge) may be used.

Intramuscular

Although Aristocort® Forte Parenteral may be administered intramuscularly for initial therapy, most physicians prefer to adjust the dose orally until adequate control is attained. Intramuscular administration provides a sustained or depot action which can be used to supplement or replace initial oral therapy. With intramuscular therapy, greater supervision of the amount of steroid used is made possible in the patient who is inconsistent in following an oral dosage schedule. In maintenance therapy, the patient-to-patient response is not uniform and, therefore, the dose must be individualized for optimal control.

The average dose is 40 mg (1 mL) administered intramuscularly once a week for conditions in which anti-inflammatory action is desired.

In general, a single parenteral dose 4 to 7 times the oral daily dose may be expected to control the patient from 4 to 7 days up to 3 to 4 weeks. Dosage should be adjusted to the point where adequate but not necessarily complete relief of symptoms is obtained.

Intra-Articular and Intrasynovial

The usual dose varies from 5 to 40 mg. The average for the knee, for example, is 25 mg. The duration of effect varies from one week to 2 months. However, acutely inflamed joints may require more frequent injections.

A lesser initial dosage range of triamcinolone diacetate injectable suspension may produce the desired effect when the drug is administered to provide a localized concentration. The site of the injection and the

volume of the injection should be carefully considered when triamcinolone diacetate is administered for this purpose.

A specific dose depends largely on the size of the joint.

Strict surgical asepsis is mandatory. The physician should be familiar with anatomical relationships as described in standard textbooks. Aristocort® Forte Parenteral may be used in any accessible joint except the intervertebrals. In general, intrasynovial therapy is suggested under the following circumstances:

1. When systemic steroid therapy is contraindicated because of side effects such as peptic ulcer.
2. When it is desirable to secure relief in one or two specific joints.
3. When good systemic maintenance fails to control flare-ups in a few joints, and it is desirable to secure relief without increasing oral therapy.

Such treatment should not be considered to constitute a cure, for although this method will ameliorate the joint symptoms, it does not preclude the need for the conventional measures usually employed.

It is suggested that infiltration of the soft tissue by local anesthetic precede intra-articular injection. A 24-gauge or larger needle on a dry syringe may be inserted into the joint and excess fluid aspirated. For the first few hours following injection, there may be local discomfort in the joint but this is usually followed rapidly by effective relief of pain and improvement in local function.

HOW SUPPLIED

Aristocort® Forte (triamcinolone diacetate injectable suspension), 40 mg/mL, parenteral, Not For Intravenous Use, supplied as follows:

NDC 0781-3037-71 40 mg/mL (1 mL Fill in a 2 mL Vial), boxes of 1

NDC 0781-3037-75 40 mg/mL (5 mL Fill in a 10 mL Vial), boxes of 1

Protect from light.

DO NOT FREEZE

SHAKE WELL

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Irreversible clumping occurs when product is frozen.

04-2014M

U46136450

Manufactured in Canada by

Sandoz Canada Inc. for

Sandoz Inc., Princeton, NJ 08540

Aristospan®
(Triamcinolone Hexacetonide Injectable Suspension, USP)
5 mg/mL PARENTERAL

NOT FOR USE IN NEWBORNS

FOR INTRALESIONAL ADMINISTRATION

NOT FOR INTRAVENOUS USE

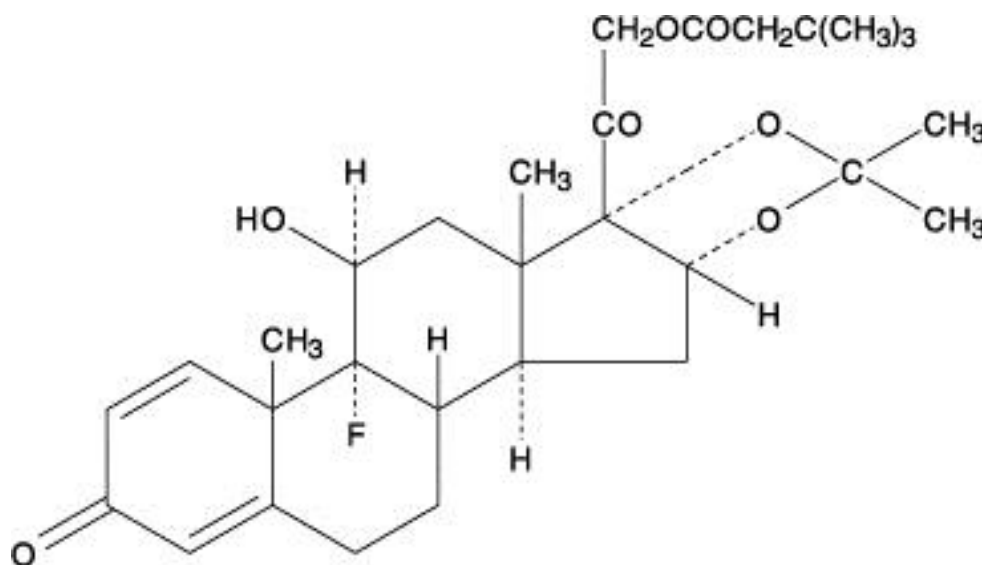
DESCRIPTION

A sterile suspension containing 5 mg/mL of micronized triamcinolone hexacetonide in the following inactive ingredients:

Polysorbate 80	0.20% w/v
Sorbitol Solution USP	50.00% w/v
Water for Injection qs ad	100.00% V
Hydrochloric Acid and Sodium Hydroxide, if required, to adjust pH to	4.0-8.0
Preservative:	
Benzyl Alcohol	0.90% w/v

Chemically triamcinolone hexacetonide USP is 9 α -Fluoro-11 β ,16 α , 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone 21-(3,3-dimethylbutyrate). The molecular weight is 532.65.

The structural formula is:



The hexacetonide ester of the glucocorticoid triamcinolone is relatively insoluble (0.0002% at 25°C in water).

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states.

Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems. When injected intralesionally or sublesionally, triamcinolone hexacetonide can be expected to be absorbed slowly from the injection site.

INDICATIONS AND USAGE

The intralesional administration of Aristospan (triamcinolone hexacetonide injectable suspension, USP) 5 mg/mL is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques; necrobiosis lipoidica diabetorum. Aristospan may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Aristospan is contraindicated in patients who are hypersensitive to any components of this product.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

This product contains benzyl alcohol. Benzyl alcohol has been associated with a fatal “Gasping Syndrome” in premature infants and infants of low birth weight.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is

not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see [PRECAUTIONS: Pediatric Use](#)).

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see [ADVERSE REACTIONS](#)).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of corticosteroids, including Aristospan®, should not be used for the treatment of traumatic brain injury.

Cardio-renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions.

There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see [PRECAUTIONS: Drug Interactions: Amphotericin B Injection and Potassium-Depleting Agents](#)).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Toxoplasma.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Reports of severe medical events have been associated with the intrathecal route of administration (see [**ADVERSE REACTIONS: Gastrointestinal**](#) and [**Neurologic/Psychiatric**](#)).

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction must be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Atrophy at the site of injection has been reported.

Cardio-renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Injection of a steroid into an infected site is to be avoided.

Neuro-psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see [DOSAGE AND ADMINISTRATION](#)).

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide

Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B Injection and Potassium-Depleting Agents

When corticosteroids are administered concomitantly with potassium-depleting agents (i. e., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics

Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, Oral

Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular Drugs

Serum concentrations of isoniazid may be decreased.

Cholestyramine

Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis Glycosides

Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including Oral Contraceptives

Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin)

Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Ketoconazole

Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal Anti-Inflammatory Agents (NSAIDs)

Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin Tests

Corticosteroids may suppress reactions to skin tests.

Vaccines

Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see [**WARNINGS: Infections: Vaccination**](#)).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see [ADVERSE REACTIONS](#)). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

(listed alphabetically, under each subsection)

Allergic Reactions

Anaphylactoid reactions, anaphylaxis, angioedema.

Cardiovascular

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see [WARNINGS](#)), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic

Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine

Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetics, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal

Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic

Negative nitrogen balance due to protein catabolism.

Musculoskeletal

Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric

Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see [WARNINGS: Infections: Neurologic](#)).

Ophthalmic

Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other

Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see [PRECAUTIONS](#))

General

The initial dosage of Aristospan (triamcinolone hexacetonide injectable suspension, USP) may vary from 2 to 48 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

It Should Be Emphasized That Dosage Requirements Are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease

entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in three or four divided doses (3.2 to 48 mg/m²bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

<i>Cortisone, 25</i>	<i>Triamcinolone, 4</i>
<i>Hydrocortisone, 20</i>	<i>Paramethasone, 2</i>
<i>Prednisolone, 5</i>	<i>Betamethasone, 0.75</i>
<i>Prednisone, 5</i>	<i>Dexamethasone, 0.75</i>
<i>Methylprednisolone, 4</i>	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

Directions for Use

Strict aseptic administration technique is mandatory.

Topical ethylchloride spray may be used locally before injection.

The syringe should be gently agitated to achieve uniform suspension before use. Since this product has been designed for ease of administration, a small bore needle (not smaller than 23 gauge) may be used.

Dilution

Aristospan suspension may also be mixed with 1% or 2% Lidocaine Hydrochloride, using the formulations which do not contain parabens. Similar local anesthetics may also be used. Diluents containing methylparaben, propylparaben, phenol, etc. should be avoided since these compounds may cause flocculation of the steroid. These dilutions will retain full potency for one week, but care should be exercised to avoid contamination of the vial's contents and the dilutions should be discarded after 7 days.

Aristospan suspension 5 mg/mL may also be diluted, if desired, with Dextrose and Sodium Chloride Injection USP, (5% and 10% Dextrose), Sodium Chloride Injection USP, or Sterile Water for Injection USP.

The optimum dilution, i.e., 1:1, 1:2, 1:4, should be determined by the nature of the lesion, its size, the depth of injection, the volume needed, and location of the lesion. In general, more superficial injections should be performed with greater dilution. Certain conditions, such as keloids, require a less dilute suspension such as 5 mg/mL, with variation in dose and dilution as dictated by the condition of the individual patient. Subsequent dosage, dilution, and frequency of injections are best judged by the clinical response.

Intralesional or Sublesional

Average Dose

Up to 0.5 mg per square inch of affected skin injected intralesionally or sublesionally. The frequency of subsequent injections is best determined by the clinical response. If desired, the vial may be diluted as indicated under **Directions for Use**.

A lesser initial dosage range of Aristospan may produce the desired effect when the drug is administered to provide a localized concentration. The site of the injection and the volume of the injection should be carefully considered when Aristospan is administered for this purpose.

HOW SUPPLIED

Aristospan® (triamcinolone hexacetonide injectable suspension, USP), 5 mg/mL is available as follows:

NDC 0781-3084-75 5 mL fill in a 10 mL vial

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Protect from light.

DO NOT FREEZE.

04-2014M

U100XXXX

Manufactured in Canada by

Sandoz Canada Inc. for

Sandoz Inc., Princeton, NJ 08540

Aristospan®
(Triamcinolone Hexacetonide Injectable Suspension, USP)
20 mg/mL PARENTERAL

NOT FOR USE IN NEWBORNS

FOR INTRA-ARTICULAR USE

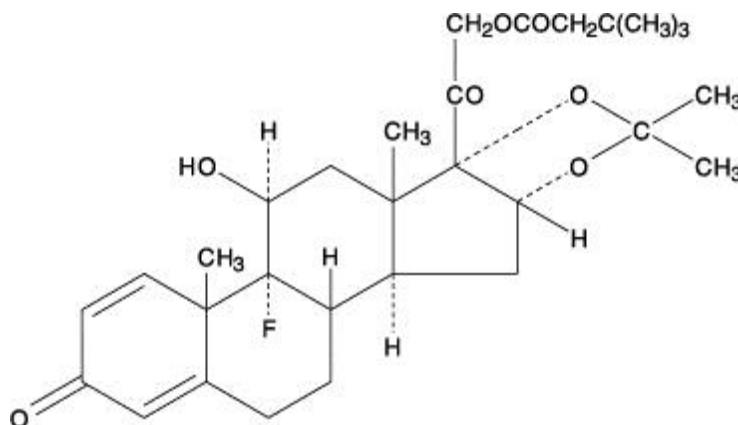
NOT FOR INTRAVENOUS USE

DESCRIPTION

A sterile suspension containing 20 mg/mL of micronized triamcinolone hexacetonide in the following inactive ingredients:

Polysorbate 80 NF	0.40% w/v
Sorbitol Solution USP	50.00% w/v
Water for Injection qs ad	100.00% V
Hydrochloric Acid and Sodium Hydroxide, if required, to adjust pH to	4.0-8.0
Preservative: Benzyl Alcohol	0.90% w/v

Chemically triamcinolone hexacetonide USP is 9 α -Fluoro-11 β ,16 α , 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone 21-(3,3-dimethylbutyrate). Molecular weight is 532.65. The structural formula is:



The hexacetonide ester of the glucocorticoid triamcinolone is relatively insoluble (0.0002% at 25°C in water).

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states.

Their synthetic analogs are primarily used for their anti-inflammatory effects in disorders of many organ systems. When injected intra-articularly, triamcinolone hexacetonide can be expected to be absorbed slowly from the injection site.

INDICATIONS AND USAGE

The intra-articular or soft tissue administration of Aristospan (triamcinolone hexacetonide injectable suspension, USP) 20 mg/mL is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis of osteoarthritis.

CONTRAINDICATIONS

Aristospan is contraindicated in patients who are hypersensitive to any components of this product.

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

This product contains benzyl alcohol. Benzyl alcohol has been associated with a fatal “Gasping Syndrome” in premature infants and infants of low birth weight.

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see [PRECAUTIONS: Pediatric Use](#)).

Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see [ADVERSE REACTIONS](#)).

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Results from one multicenter, randomized, placebo controlled study with methylprednisolone hemisuccinate, an IV corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of corticosteroids, including Aristospan®, should not be used for the treatment of traumatic brain injury.

Cardio-renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions.

There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see [PRECAUTIONS: Drug Interactions: Amphotericin B Injection and Potassium-Depleting Agents](#)).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known.

If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Reports of severe medical events have been associated with the intrathecal route of administration (see [ADVERSE REACTIONS: Gastrointestinal](#) and [Neurologic/Psychiatric](#)).

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or

viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroids should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Atrophy at the site of injection has been reported.

Cardio-renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcer, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Intra-articular and Soft Tissue Administration

Intra-articularly injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Corticosteroid injection into unstable joints is generally not recommended.

Intra-articular injection may result in damage to joint tissues (see [ADVERSE REACTIONS: Musculoskeletal](#)).

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Neuro-psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see [DOSAGE AND ADMINISTRATION](#)).

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide

Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B Injection and Potassium-Depleting Agents

When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics

Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, Oral

Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular Drugs

Serum concentrations of isoniazid may be decreased.

Cholestyramine

Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine

Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis Glycosides

Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including Oral Contraceptives

Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers (e.g., barbiturates, phenytoin, carbamazepine, rifampin)

Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Ketoconazole

Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal Anti-Inflammatory Agents (NSAIDs)

Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin Tests

Corticosteroids may suppress reactions to skin tests.

Vaccines

Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see [**WARNINGS: Infections: Vaccination**](#)).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects

Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see [ADVERSE REACTIONS](#)). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered

corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

(listed alphabetically, under each subsection)

Allergic Reactions

Anaphylactoid reactions, anaphylaxis, angioedema.

Cardiovascular

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see [WARNINGS](#)), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic

Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine

Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetics, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness, (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal

Abdominal distention, bowel/bladder dysfunction (after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic

Negative nitrogen balance due to protein catabolism.

Musculoskeletal

Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, postinjection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric

Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration (see [WARNINGS: Infections: Neurologic](#)).

Ophthalmic

Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other

Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

NOTE: CONTAINS BENZYL ALCOHOL (see [PRECAUTIONS](#))

General

The initial dosage of Aristospan (triamcinolone hexacetonide injectable suspension, USP) may vary from 2 to 48 mg per day depending on the specific disease entity being treated. However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

It Should Be Emphasized That Dosage Requirements are Variable and Must Be Individualized on the Basis of the Disease Under Treatment and the Response of the Patient. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in three or four divided doses (3.2 to 48 mg/m²bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

<i>Cortisone, 25</i>	<i>Triamcinolone, 4</i>
<i>Hydrocortisone, 20</i>	<i>Paramethasone, 2</i>
<i>Prednisolone, 5</i>	<i>Betamethasone, 0.75</i>
<i>Prednisone, 5</i>	<i>Dexamethasone, 0.75</i>
<i>Methylprednisolone, 4</i>	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

Directions for Use

Strict aseptic administration technique is mandatory.

Topical ethylchloride spray may be used locally before injection.

The syringe should be gently agitated to achieve uniform suspension before use. Since this product has been designed for ease of administration, a small bore needle (not smaller than 23 gauge) may be used.

Dilution

Aristospan suspension may be mixed with 1% or 2% Lidocaine Hydrochloride, using the formulations which do not contain parabens. Similar local anesthetics may also be used. Diluents containing methylparaben, propylparaben, phenol, etc., should be avoided since these compounds may cause

flocculation of the steroid. These dilutions will retain full potency for one week, but care should be exercised to avoid contamination of the vial's contents and the dilutions should be discarded after 7 days.

Intra-articular

Average dose - 2 to 20 mg (0.1 mL to 1 mL)

The dose depends on the size of the joint to be injected, the degree of inflammation, and the amount of fluid present. In general, large joints (such as knee, hip, shoulder) require 10 to 20 mg. For small joints (such as interphalangeal, metacarpophalangeal), 2 to 6 mg, may be employed. When the amount of synovial fluid is increased, aspiration may be performed before administering Aristospan. Subsequent dosage and frequency of injection can best be judged by clinical response.

The usual frequency of injection into a single joint is every three or four weeks, and injection more frequently than that is generally not advisable. To avoid possible joint destruction from repeated use of intra-articular corticosteroids, injection should be as infrequent as possible, consistent with adequate patient care. Attention should be paid to avoiding deposition of drug along the needle path which might produce atrophy.

HOW SUPPLIED

Aristospan® (triamcinolone hexacetonide injectable suspension, USP), 20 mg/mL is available as follows:

NDC 0781-3085-71 1 mL fill in a 2 mL vial

NDC 0781-3085-75 5 mL fill in a 10 mL vial

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Protect from light.

DO NOT FREEZE.

04-2014M

46136451

Manufactured in Canada by

Sandoz Canada Inc. for

Sandoz Inc., Princeton, NJ 08540

KENALOG[®]-10 INJECTION

(triamcinolone acetonide injectable suspension, USP)

NOT FOR USE IN NEONATES

CONTAINS BENZYL ALCOHOL

For Intra-articular or Intralesional Use Only

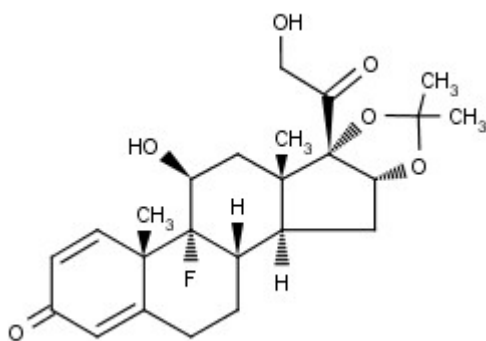
NOT FOR INTRAVENOUS, INTRAMUSCULAR, INTRAOCULAR, EPIDURAL, OR INTRATHECAL USE

DESCRIPTION

Kenalog[®]-10 Injection (triamcinolone acetonide injectable suspension, USP) is triamcinolone acetonide, a synthetic glucocorticoid corticosteroid with marked anti-inflammatory action, in a sterile aqueous suspension suitable for intralesional and intra-articular injection. THIS FORMULATION IS SUITABLE FOR INTRA-ARTICULAR AND INTRALESIONAL USE ONLY.

Each mL of the sterile aqueous suspension provides 10 mg triamcinolone acetonide, with 0.65% sodium chloride for isotonicity, 0.9% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80; sodium hydroxide or hydrochloric acid may have been added to adjust pH between 5.0 and 7.5. At the time of manufacture, the air in the container is replaced by nitrogen.

The chemical name for triamcinolone acetonide is 9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. Its structural formula is:



MW 434.50

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Synthetic analogs such as triamcinolone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

INDICATIONS AND USAGE

The intra-articular or soft tissue administration of Kenalog-10 Injection (triamcinolone acetonide injectable suspension, USP) is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis, or osteoarthritis.

The intralesional administration of Kenalog-10 Injection is indicated for alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and psoriatic plaques; necrobiosis lipoidica diabetorum. Kenalog-10 Injection may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

CONTRAINDICATIONS

Kenalog-10 Injection is contraindicated in patients who are hypersensitive to any components of this product (see **WARNINGS: General**).

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids (see **WARNINGS: Neurologic**). Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS: Pediatric Use**).

Because Kenalog-10 Injection (triamcinolone acetonide injectable suspension, USP) is a suspension, it should *not* be administered intravenously. Strict aseptic technique is mandatory.

Rare instances of anaphylaxis have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**). Cases of serious anaphylaxis, including death, have been reported

in individuals receiving triamcinolone acetonide injection, regardless of the route of administration.

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.

Kenalog-10 Injection is a long-acting preparation, and is *not* suitable for use in acute stress situations.

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an intravenous corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including Kenalog-10 Injection, should not be used for the treatment of traumatic brain injury.

Cardio-Renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when they are used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **PRECAUTIONS: Drug Interactions: Amphotericin B injection and potassium-depleting agents**).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, or *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, eg, for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration (see **ADVERSE REACTIONS: Gastrointestinal and Neurologic/Psychiatric**).

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

Adequate studies to demonstrate the safety of Kenalog Injection use by intratubal, subconjunctival, sub-Tenons, retrobulbar, and intraocular (intravitreal) injections have not been performed. Endophthalmitis, eye inflammation, increased intraocular pressure, and visual disturbances including vision loss have been reported with intravitreal administration. Administration of Kenalog Injection intraocularly or into the nasal turbinates is not recommended.

Intraocular injection of corticosteroid formulations containing benzyl alcohol, such as Kenalog Injection, is not recommended because of potential toxicity from the benzyl alcohol.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-Renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy

should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Intra-Articular and Soft Tissue Administration

Intra-articularly injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Corticosteroid injection into unstable joints is generally not recommended.

Intra-articular injection may result in damage to joint tissues (see **ADVERSE REACTIONS: Musculoskeletal**).

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (ie, decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special

consideration should be given to patients at increased risk of osteoporosis (ie, postmenopausal women) before initiating corticosteroid therapy.

Neuro-Psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychiatric derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (ie, amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic enzyme inducers (eg, barbiturates, phenytoin, carbamazepine, rifampin): Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Ketoconazole: Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory drugs) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS: Infections: Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome,” the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, eg, severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any

route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (ie, cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

(listed alphabetically under each subsection)

The following adverse reactions may be associated with corticosteroid therapy:

Allergic reactions: Anaphylaxis including death, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, lupus erythematosus-like lesions, purpura, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic

agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration [see **WARNINGS: Neurologic**]), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, post injection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychiatric disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration. Spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke (including brainstem) have been reported after epidural administration of corticosteroids (see **WARNINGS: Serious Neurologic Adverse Reactions with Epidural Administration** and **WARNINGS: Neurologic**).

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

General

NOTE: CONTAINS BENZYL ALCOHOL (see [PRECAUTIONS](#)).

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in 3 or 4 divided doses (3.2 to 48 mg/m²bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

<i>Cortisone, 25</i>	<i>Triamcinolone, 4</i>
<i>Hydrocortisone, 20</i>	<i>Paramethasone, 2</i>
<i>Prednisolone, 5</i>	<i>Betamethasone, 0.75</i>
<i>Prednisone, 5</i>	<i>Dexamethasone, 0.75</i>
<i>Methylprednisolone, 4</i>	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

Intra-Articular Administration

Dosage

The initial dose of Kenalog-10 Injection for intra-articular administration may vary from 2.5 mg to 5 mg for smaller joints and from 5 mg to 15 mg for larger joints, depending on the specific disease entity being treated. Single injections into several joints, up to a total of 20 mg or more, have been given.

Intralesional

For intralesional administration, the initial dose per injection site will vary depending on the specific disease entity and lesion being treated. The site of injection and volume of injection should be carefully considered due to the potential for cutaneous atrophy.

Multiple sites separated by one centimeter or more may be injected, keeping in mind that the greater the *total* volume employed the more corticosteroid becomes available for systemic absorption and systemic effects. Such injections may be repeated, if necessary, at weekly or less frequent intervals.

Localization of Doses

The lower dosages in the initial dosage range of triamcinolone acetonide may produce the desired effect when the corticosteroid is administered to provide a localized concentration. The site and volume of the injection should be carefully considered when triamcinolone acetonide is administered for this purpose.

Administration

STRICT ASEPTIC TECHNIQUE IS MANDATORY. The vial should be shaken before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used. After withdrawal, inject without delay to prevent settling in the syringe.

Injection Technique

For treatment of joints, the usual intra-articular injection technique should be followed. If an excessive amount of synovial fluid is present in the joint, some, but not all, should be aspirated to aid in the relief of pain and to prevent undue dilution of the steroid.

With intra-articular administration, prior use of a local anesthetic may often be desirable. Care should be taken with this kind of injection, particularly in the deltoid region, to avoid injecting the suspension into the tissues surrounding the site, since this may lead to tissue atrophy.

In treating acute nonspecific tenosynovitis, care should be taken to ensure that the injection of Kenalog-10 Injection is made into the tendon sheath rather than the tendon substance. Epicondylitis may be treated by infiltrating the preparation into the area of greatest tenderness.

Intralesional

For treatment of dermal lesions, Kenalog-10 Injection should be injected directly into the lesion, ie, intradermally or subcutaneously. For accuracy of dosage measurement and ease of administration, it is preferable to employ a tuberculin syringe and a small-bore needle (23-25 gauge). Ethyl chloride spray may be used to alleviate the discomfort of the injection.

HOW SUPPLIED

Kenalog[®]-10 Injection (triamcinolone acetonide injectable suspension, USP) is supplied in 5 mL multiple-dose vials (NDC 0003-0494-20) providing 10 mg triamcinolone acetonide per mL.

Storage

Store at controlled room temperature, 20°–25°C (68°–77°F), avoid freezing and protect from light. Do not refrigerate.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
Product of Italy

Rev July 2014

KENALOG[®]-40 INJECTION

(triamcinolone acetonide injectable suspension, USP)

NOT FOR USE IN NEONATES
CONTAINS BENZYL ALCOHOL

For Intramuscular or Intra-articular Use Only

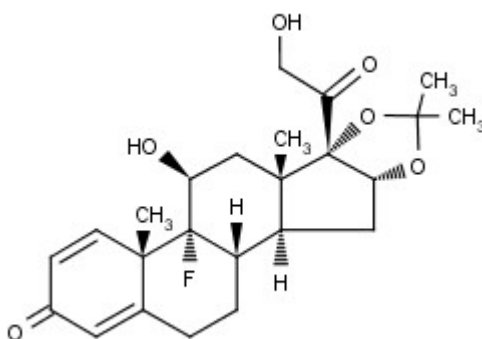
**NOT FOR INTRAVENOUS, INTRADERMAL, INTRAOCULAR, EPIDURAL,
OR INTRATHECAL USE**

DESCRIPTION

Kenalog[®]-40 Injection (triamcinolone acetonide injectable suspension, USP) is a synthetic glucocorticoid corticosteroid with anti-inflammatory action. THIS FORMULATION IS SUITABLE FOR INTRAMUSCULAR AND INTRA-ARTICULAR USE ONLY. THIS FORMULATION IS NOT FOR INTRADERMAL INJECTION.

Each mL of the sterile aqueous suspension provides 40 mg triamcinolone acetonide, with 0.65% sodium chloride for isotonicity, 0.99% (w/v) benzyl alcohol as a preservative, 0.75% carboxymethylcellulose sodium, and 0.04% polysorbate 80. Sodium hydroxide or hydrochloric acid may be present to adjust pH to 5.0 to 7.5. At the time of manufacture, the air in the container is replaced by nitrogen.

The chemical name for triamcinolone acetonide is 9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. Its structural formula is:



MW 434.50

1

Triamcinolone acetonide occurs as a white to cream-colored, crystalline powder having not more than a slight odor and is practically insoluble in water and very soluble in alcohol.

CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract.

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Synthetic analogs such as triamcinolone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Kenalog-40 Injection has an extended duration of effect which may be sustained over a period of several weeks. Studies indicate that following a single intramuscular dose of 60 mg to 100 mg of triamcinolone acetonide, adrenal suppression occurs within 24 to 48 hours and then gradually returns to normal, usually in 30 to 40 days. This finding correlates closely with the extended duration of therapeutic action achieved with the drug.

INDICATIONS AND USAGE

Intramuscular

Where oral therapy is not feasible, injectable corticosteroid therapy, including Kenalog-40 Injection (triamcinolone acetonide injectable suspension, USP) is indicated **for intramuscular use** as follows:

Allergic states: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, serum sickness, transfusion reactions.

Dermatologic diseases: Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsuppurative thyroiditis.

Gastrointestinal diseases: To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic disorders: Acquired (autoimmune) hemolytic anemia, Diamond-Blackfan anemia, pure red cell aplasia, selected cases of secondary thrombocytopenia.

Miscellaneous: Trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic diseases: For the palliative management of leukemias and lymphomas.

Nervous system: Acute exacerbations of multiple sclerosis; cerebral edema associated with primary or metastatic brain tumor or craniotomy.

Ophthalmic diseases: Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.

Renal diseases: To induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.

Respiratory diseases: Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.

Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis; acute rheumatic carditis; ankylosing spondylitis; psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

Intra-Articular

The **intra-articular or soft tissue administration** of Kenalog-40 Injection is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis, or osteoarthritis.

CONTRAINDICATIONS

Kenalog-40 Injection is contraindicated in patients who are hypersensitive to any components of this product (see **WARNINGS: General**).

Intramuscular corticosteroid preparations are contraindicated for idiopathic thrombocytopenic purpura.

WARNINGS

Serious Neurologic Adverse Reactions with Epidural Administration

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids (see **WARNINGS: Neurologic**). Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

General

Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or

other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **PRECAUTIONS: Pediatric Use**).

Rare instances of anaphylaxis have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**). Cases of serious anaphylaxis, including death, have been reported in individuals receiving triamcinolone acetonide injection, regardless of the route of administration.

Because Kenalog-40 Injection (triamcinolone acetonide injectable suspension, USP) is a suspension, it should **not** be administered intravenously.

Unless a **deep** intramuscular injection is given, local atrophy is likely to occur. (For recommendations on injection techniques, see **DOSAGE AND ADMINISTRATION**.) Due to the significantly higher incidence of local atrophy when the material is injected into the deltoid area, this injection site should be avoided in favor of the gluteal area.

Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation. Kenalog-40 Injection is a long-acting preparation, and is not suitable for use in acute stress situations. To avoid drug-induced adrenal insufficiency, supportive dosage may be required in times of stress (such as trauma, surgery, or severe illness) both during treatment with Kenalog-40 Injection and for a year afterwards.

Results from one multicenter, randomized, placebo-controlled study with methylprednisolone hemisuccinate, an intravenous corticosteroid, showed an increase in early (at 2 weeks) and late (at 6 months) mortality in patients with cranial trauma who were determined not to have other clear indications for corticosteroid treatment. High doses of systemic corticosteroids, including Kenalog-40 Injection, should not be used for the treatment of traumatic brain injury.

Cardio-Renal

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when they are used in large doses. Dietary salt restriction and potassium supplementation may be necessary (see **PRECAUTIONS**). All corticosteroids increase calcium excretion.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Endocrine

Corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections

General

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.

Fungal Infections

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **PRECAUTIONS: Drug Interactions:** *Amphotericin B injection and potassium-depleting agents*).

Special Pathogens

Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, or *Toxoplasma*.

It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis

The use of corticosteroids in patients with active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, eg, for Addison's disease.

Viral Infections

Chicken pox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the

underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents should be considered.

Neurologic

Epidural and intrathecal administration of this product is not recommended. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration (see **ADVERSE REACTIONS: Gastrointestinal and Neurologic/Psychiatric**).

Ophthalmic

Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

Adequate studies to demonstrate the safety of Kenalog Injection use by intratubinal, subconjunctival, sub-Tenons, retrobulbar, and intraocular (intravitreal) injections have not been performed. Endophthalmitis, eye inflammation, increased intraocular pressure, and visual disturbances including vision loss have been reported with intravitreal administration. Administration of Kenalog Injection intraocularly or into the nasal turbinates is not recommended.

Intraocular injection of corticosteroid formulations containing benzyl alcohol, such as Kenalog Injection, is not recommended because of potential toxicity from the benzyl alcohol.

PRECAUTIONS

General

This product, like many other steroid formulations, is sensitive to heat. Therefore, it should not be autoclaved when it is desirable to sterilize the exterior of the vial.

The lowest possible dose of corticosteroid should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-Renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Intra-Articular and Soft Tissue Administration

Intra-articularly injected corticosteroids may be systemically absorbed.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

Injection of a steroid into an infected site is to be avoided. Local injection of a steroid into a previously infected joint is not usually recommended.

Corticosteroid injection into unstable joints is generally not recommended.

Intra-articular injection may result in damage to joint tissues (see **ADVERSE REACTIONS: Musculoskeletal**).

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (ie, decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (ie, postmenopausal women) before initiating corticosteroid therapy.

Neuro-Psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and

respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychiatric derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision, to advise any medical attendants that they are taking corticosteroids, and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

Aminoglutethimide: Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (ie, amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic enzyme inducers (eg, barbiturates, phenytoin, carbamazepine, rifampin): Drugs which induce hepatic microsomal drug metabolizing enzyme activity may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased.

Ketoconazole: Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory drugs) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with

corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Vaccines: Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible (see **WARNINGS: Infections: Vaccination**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects: Pregnancy Category C

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when corticosteroids are administered to a nursing woman.

Pediatric Use

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gasping syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome,” the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). Other indications for pediatric use of corticosteroids, eg, severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (ie, cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of

systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

(listed alphabetically under each subsection)

The following adverse reactions may be associated with corticosteroid therapy:

Allergic reactions: Anaphylaxis including death, angioedema.

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS**), pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scaly skin, ecchymoses and petechiae, edema, erythema, hyperpigmentation, hypopigmentation, impaired wound healing, increased sweating, lupus erythematosus-like lesions, purpura, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in

times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and electrolyte disturbances: Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Abdominal distention, bowel/bladder dysfunction (after intrathecal administration [see **WARNINGS: Neurologic**]), elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, calcinosis (following intra-articular or intralesional use), Charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, post injection flare (following intra-articular use), steroid myopathy, tendon rupture, vertebral compression fractures.

Neurologic/Psychiatric: Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychiatric disorders, vertigo. Arachnoiditis, meningitis, paraparesis/paraplegia, and sensory disturbances have occurred after intrathecal administration. Spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke (including brainstem) have been reported after epidural administration of corticosteroids (see **WARNINGS: Serious Neurologic Adverse Reactions with Epidural Administration** and **WARNINGS: Neurologic**).

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts, rare instances of blindness associated with periocular injections.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE

Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

General

NOTE: CONTAINS BENZYL ALCOHOL (see PRECAUTIONS).

The initial dose of Kenalog-40 Injection may vary from 2.5 mg to 100 mg per day depending on the specific disease entity being treated (see **Dosage** section below). However, in certain overwhelming, acute, life-threatening situations, administration in dosages exceeding the usual dosages may be justified and may be in multiples of the oral dosages.

IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.

After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

Dosage

SYSTEMIC

The suggested initial dose is 60 mg, **injected deeply into the gluteal muscle**. Atrophy of subcutaneous fat may occur if the injection is not properly given. Dosage is usually adjusted within the range of 40 mg to 80 mg, depending upon patient response and duration of relief. However, some patients may be well controlled on doses as low as 20 mg or less.

Hay fever or pollen asthma: Patients with hay fever or pollen asthma who are not responding to pollen administration and other conventional therapy may obtain a remission of symptoms lasting throughout the pollen season after a single injection of 40 mg to 100 mg.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 160 mg of triamcinolone for a week followed by 64 mg every other day for one month are recommended (see **PRECAUTIONS: Neuro-Psychiatric**).

In pediatric patients, the initial dose of triamcinolone may vary depending on the specific disease entity being treated. The range of initial doses is 0.11 to 1.6 mg/kg/day in 3 or 4 divided doses (3.2 to 48 mg/m²bsa/day).

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

<i>Cortisone, 25</i>	<i>Triamcinolone, 4</i>
<i>Hydrocortisone, 20</i>	<i>Paramethasone, 2</i>
<i>Prednisolone, 5</i>	<i>Betamethasone, 0.75</i>
<i>Prednisone, 5</i>	<i>Dexamethasone, 0.75</i>
<i>Methylprednisolone, 4</i>	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

LOCAL

Intra-articular administration: A single local injection of triamcinolone acetonide is frequently sufficient, but several injections may be needed for adequate relief of symptoms.

Initial dose: 2.5 mg to 5 mg for smaller joints and from 5 mg to 15 mg for larger joints, depending on the specific disease entity being treated. For adults, doses up to 10 mg for smaller areas and up to 40 mg for larger areas have usually been sufficient. Single injections into several joints, up to a total of 80 mg, have been given.

Administration

GENERAL

STRICT ASEPTIC TECHNIQUE IS MANDATORY. The vial should be shaken before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used. After withdrawal, Kenalog-40 Injection should be injected without delay to prevent settling in the syringe. Careful technique should be employed to avoid the possibility of entering a blood vessel or introducing infection.

SYSTEMIC

For systemic therapy, injection should be made **deeply into the gluteal muscle** (see **WARNINGS**). For adults, a minimum needle length of 1½ inches is recommended. In obese patients, a longer needle may be required. Use alternative sites for subsequent injections.

LOCAL

For treatment of joints, the usual intra-articular injection technique should be followed. If an excessive amount of synovial fluid is present in the joint, some, but not all, should be aspirated to aid in the relief of pain and to prevent undue dilution of the steroid.

With intra-articular administration, prior use of a local anesthetic may often be desirable. Care should be taken with this kind of injection, particularly in the deltoid region, to avoid injecting the suspension into the tissues surrounding the site, since this may lead to tissue atrophy.

In treating acute nonspecific tenosynovitis, care should be taken to ensure that the injection of the corticosteroid is made into the tendon sheath rather than the tendon substance. Epicondylitis may be treated by infiltrating the preparation into the area of greatest tenderness.

HOW SUPPLIED

Kenalog[®]-40 Injection (triamcinolone acetonide injectable suspension, USP) is supplied in vials providing 40 mg triamcinolone acetonide per mL.

40 mg/mL, 1 mL vial	NDC 0003-0293-05
40 mg/mL, 5 mL vial	NDC 0003-0293-20
40 mg/mL, 10 mL vial	NDC 0003-0293-28

Storage

Store at controlled room temperature, 20°–25°C (68°–77°F), avoid freezing and protect from light. Do not refrigerate.

Bristol-Myers Squibb Company
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Product of Italy

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