Subject: Updated Information Regarding Administration of Hexatrione 2% (triamcinolone hexacetonide), injectable suspension (intra-articular), 20 mg/mL

Dear Healthcare Professional:

In order to address ongoing shortage of Aristospa® (triamcinolone hexacetonide injectable suspension, USP), 20 mg/mL, Medexus Pharma Incorporated (Medexus) is coordinating with the U.S. Food and Drug Administration (FDA) to import Hexatrione 2% (triamcinolone hexacetonide), injectable suspension (intra-articular), 20 mg/mL, manufactured and marketed in France by Ethypharm Laboratories. Hexatrione 2% (triamcinolone hexacetonide) is supplied in an auto-breakable pre-scored One Point Cut (OPC) ampoule. Please read this entire letter for updates regarding administration of this ampoule.

At this time, no other entity except Medexus is authorized by the FDA to import or distribute triamcinolone hexacetonide injectable suspension in the U.S. FDA has not approved Medexus’ Hexatrione 2% (triamcinolone hexacetonide) injectable suspension in the United States.

Effective immediately, and during this temporary period, Medexus will offer the following presentation of Triamcinolone Hexacetonide Injectable Suspension:

<table>
<thead>
<tr>
<th>Product name and description</th>
<th>Size</th>
<th>Package</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexatrione 2% Injectable Suspension (INTRA-ARTICULAR), 40 mg per ampoule (20 mg/ml)</td>
<td>2 mL ampoule</td>
<td>one ampoule per carton</td>
<td>59137-570-01</td>
</tr>
</tbody>
</table>

There are **key differences between the labeling of the FDA approved Aristospa® (triamcinolone hexacetonide injectable suspension) and Medexus’ imported Hexatrione 2% (triamcinolone hexacetonide), injectable suspension (intra-articular).** It is important to note the following:

- Medexus’s imported product triamcinolone hexacetonide strength is labeled 40mg per ampoule (20mg/ml).

- The imported product is packaged as a 2 mL ampule with a total strength of 40 mg/2 mL. Each mL contains 20 mg of triamcinolone hexacetonide. The US approved product, Aristospa®, was available as a 1 mL vial with a total strength of 20 mg/mL.

- **The imported product does not have a barcode.** Institutions should manually input the product into their systems to confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.
• The imported product contains the same concentration of active substance as Aristospan® (Triamcinolone Hexacetonide Injectable Suspension, USP), 20 mg/mL and the same composition of excipients.

• Hexatrione 2% (triamcinolone hexacetonide), injectable suspension is a suspension of milky white appearance, with no apparent crystalline formation. Each unit of Hexatrione 2% is composed of a 2 mL suspension of triamcinolone hexacetonide at 20 mg/mL.

• Hexatrione 2% should not be diluted before injection.

• Hexatrione is supplied via an auto-breakable pre-scored One Point Cut (OPC) ampoule. OPC ampoules can be opened easily and safely, reducing the risk of splintering and/or sharp edges (Instructions for opening One Point Cut ampoules attached at the end of this letter).

• Hexatrione is a suspension of milky white appearance and due to its formulation properties, a filtered needle is not recommended. Filter needles used with certain medications, such as suspensions and liposomal formulations can remove important active ingredients that are suspended in the vehicle. Do not use the medicine if the ampoule shatters or if the opened ampoule is contaminated with glass after opening.

• For intra-articular use, it is recommended to use a needle bore gauge between 19 and 25. Viscosity of the suspension is a major factor in needle size selection. The active molecule is less than 260 µm so a 23 g or 25 G needle with internal diameters ranging from 337 to 260 µm would suffice, however, the pull becomes more difficult with the smaller 25G needle.

Some of the key differences in the labeling between US approved Aristospan® and the imported product, Hexatrione 2% is displayed in the **product comparison** table at the end of this letter, which also includes images of the labels for your reference.

Please refer to the enclosed FDA approved package insert for the Aristospan® 20 mg/mL drug product and the English translated package insert for Hexatrione 2% drug product for full prescribing information.

**To order or if you have questions** about Hexatrione 2% (triamcinolone hexacetonide), injectable suspension, please contact Medexus’ Customer Service by phone at 1-855-336-3322 (Option 9).

Healthcare providers and patients are encouraged to report adverse events or quality problems experienced with the use of this product, call Medexus’ Medical Affairs at 1-855-336-3322, Monday-Friday, between the hours of 8 A.M. and 6 P.M. (EST).

Adverse events, medication errors, or quality problems experienced with the use of this product may also be reported to FDA’s MedWatch Adverse Reporting Program either online, by regular mail or by fax:

• Complete and submit the report **Online**: [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)
• **Regular Mail or Fax:** Download form [www.fda.gov/MedWatch/getforms.htm](http://www.fda.gov/MedWatch/getforms.htm) or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178 (1-800-332-0178)

If you have any questions about the information contained in this letter or use of Hexatrione 2% (triamcinolone hexacetonide), injectable suspension, please contact Medexus’ Medical Affairs at 1-855-336-3322.

Sincerely,

Khaled M Mohamed
Director, Regulatory Affairs
<table>
<thead>
<tr>
<th><strong>Product Comparison Table</strong></th>
</tr>
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<tbody>
<tr>
<td><strong>US Approved Product</strong></td>
</tr>
<tr>
<td><strong>Product Name</strong></td>
</tr>
<tr>
<td><strong>Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)</strong></td>
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<tr>
<td><strong>Dosage Form(s)</strong></td>
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<tr>
<td><strong>Strength(s)</strong></td>
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<tr>
<td><strong>Formulation</strong></td>
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<tr>
<td>Triamcinolone hexacetonide</td>
</tr>
<tr>
<td>Sorbitol</td>
</tr>
<tr>
<td>Polysorbate 80</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
</tr>
<tr>
<td>Water for injection</td>
</tr>
<tr>
<td><strong>Container Closure System</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Indications and Usage</strong></td>
</tr>
<tr>
<td>Description</td>
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<td>-------------</td>
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<tr>
<td><strong>Dosage and Administration:</strong> <strong>Dilution</strong></td>
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<tr>
<td><strong>Storage Conditions</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
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</tbody>
</table>
Aristospan®
(triamcinolone hexacetonide injectable suspension, USP)

20 mg/mL
Sterile

FOR INTRA-ARTICULAR USE
NOT FOR INTRAVENOUS USE
PROTECT FROM LIGHT.
SHAKE WELL.
Rx only  1 mL Vial
Mfd. in Canada by Sandoz
Canada, Inc. for Sandoz Inc.,
Princeton, NJ 08540

HEXATRIONE®
2 PERCENT
Injectable suspension
Intra-articular
Triamcinolone Hexacetonide
2-mL (Glass) Ampoule
(20mg / mL)

ONLY FOR INTRA-ARTICULAR ADMINISTRATION

Respect prescribed doses
List 1-Only under prescription

Lot: DMA86
Exp: 03-2023

L100233
Aristospan®
(triamcinolone hexacetonide injectable suspension, USP)

**NDC 0781-3085-71**

20 mg/mL

**NDC 0781-3085-75**

100 mg/5 mL

(20 mg/mL)

FOR INTRA-ARTICULAR USE
NOT FOR INTRAVENOUS USE
SHAKE WELL
STERILE

Rx only
1 mL Vial
SANDOZ

Rx only
5 mL Vial
SANDOZ

Each mL contains:
20 mg of triamcinolone hexacetonide
Average Adult Intra-Articular Dosage: 2 to 20 mg every three weeks (see package insert)

Inactive Ingredients: Polysorbate 80 (0.40%), sorbitol solution 50%, water for injection q.s. 100%, hydrochloric acid and sodium hydroxide, if required, to adjust pH to 4.0-6.0

Preservative: Benzy alcohol 0.90%. Store at 20°C to 25°C (68°F-77°F) (see USP Controlled Room Temperature), DO NOT FREEZE. PROTECT FROM LIGHT. SHAKE WELL.

Manufactured in Canada by SANDOZ CANADA INC.
For SANDOZ INC., Princeton, NJ 08540

EDP 05-10-07

HEXATRIONE 2%

Injectable Suspension

Each mL of HEXATRIONE contains 20mg triamcinolone hexacetonide.

Inactive ingredients:
- Benzy alcohol
- Polysorbate 80, sorbitol at 70%, water for injection, if necessary
- Sodium hydrogen and hydrochloric acid for pH adjustment.

For single use only.
Keep out of the reach of children.
Contains Benzy Alcohol as aPreservative.

Store below 30°C (86°F) Protect from light.

NDC 58137-570-81
CIN 10016
Each mL contains: triamcinolone hexacetonide 20 mg

**Inactive Ingredients:**
Polysorbate 80 0.40%, sorbitol solution 50%, water for injection q.s. 100%, hydrochloric acid and sodium hydroxide, if required, to adjust pH to 4.0-8.0.
Preservative: Benzy alcohol 0.90%.

**EACH mL OF HEXATRIONE**

contains 20mg triamcinolone hexacetonide.

**Inactive ingredients:**
benzyl alcohol, polysorbate 80, sorbitol at 70%, water for injection, if necessary, sodium hydroxide and hydrochloric acid for pH adjustment.

For single use only.
Keep out of the reach of children.

Contains Benzy Alcohol as a Preservative.
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:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 80 NF</td>
<td>0.40% w/v</td>
</tr>
<tr>
<td>Sorbitol Solution USP</td>
<td>50.00% w/v</td>
</tr>
<tr>
<td>Water for Injection qs ad</td>
<td>100.00% V</td>
</tr>
<tr>
<td>Hydrochloric Acid and Sodium Hydroxide, if required, to adjust pH to</td>
<td>4.0-8.0</td>
</tr>
<tr>
<td>Preservative: Benzyl Alcohol</td>
<td>0.90% w/v</td>
</tr>
</tbody>
</table>

Chemically triamcinolone hexacetonide USP is 9α-Fluoro-11β,16α,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:

![Structural formula of triamcinolone hexacetonide](image)

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).

Reference ID: 3536958
**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.

Amphoterin 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 “gassing 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 “gassing 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.

Reference ID: 3536958
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:

<table>
<thead>
<tr>
<th>Cortisone, 25</th>
<th>Triamcinolone, 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone, 20</td>
<td>Paramethasone, 2</td>
</tr>
<tr>
<td>Prednisolone, 5</td>
<td>Betamethasone, 0.75</td>
</tr>
<tr>
<td>Prednisone, 5</td>
<td>Dexamethasone, 0.75</td>
</tr>
<tr>
<td>Methylprednisolone, 4</td>
<td></td>
</tr>
</tbody>
</table>

*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
floculation 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.**
1. WHAT IS HEXATRIONE 2 PERCENT, suspension for injection (intra-articular) and WHAT IT IS USED FOR?

Hexatrione contains benzyl alcohol and should be used with caution when the condition justifies a strong local concentration. Prior to local injection consider the risk of infection, in particular the risk of promoting bacterial proliferation. This product is indicated in rheumatological disorders by intra-articular injections: inflammatory arthritis (adult forms), juvenile idiopathic arthritis (children and adolescents), acute forms of inflammatory arthritis.

2. PRECAUTIONS AND METHOD OF ADMINISTRATION

Intra-articular route

3. HOW TO USE HEXATRIONE 2 PERCENT, suspension for injection (intra-articular) - Adverse reactions

1. This booklet contains:
   1. Name of the drug
   2. What you need to know before using HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)?

2. Name of the drug

HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)

Transmicronhexionate

Read all of this leaflet carefully before using this medicine because it contains important information for you.

- Keep this leaflet. You might need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed. Do not give this to anyone else. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This also applies to any side effects that are not mentioned in this leaflet. See section 4.

What does this booklet contain?

1. What is HEXATRIONE 2 PERCENT, suspension for injection (intra-articular) and in which cases is it used?

2. In children and adolescents unless your doctor otherwise recommends, due to the presence of benzyl alcohol.

3. How to use HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)?

4. What are the possible side effects?

5. How to store HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)?

6. Contents of the pack and other information:

What is this leaflet for?

- The benefit / risk ratio must be carefully evaluated before any administration of hexatrione in children under 3 years of age, taking into account the presence of benzyl alcohol which can induce toxic reactions, due to a possible neurological tropism.
- Due to a potential systemic absorption, certain contraindications for systemic corticosteroids must be taken into account, in particular if the injections are multiple (several locations) or repeated in the short term:
  - Certain viral disease (including hepatitis, herpes, chickenpox, shingles)
  - Psychiatric states not controlled by treatment,
  - Use vaccines.
- Corticosteroid therapy can promote the occurrence of various infectious complications. Multiple (multiple locations) or repeated short-term injections may cause clinical and laboratory symptoms of hydrocortisolism.
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. If you have liver or kidney disease, Ask your doctor or pharmacist before you are pregnant or breast-feeding. If you have liver or kidney disease.
- Large amounts of benzyl alcohol can build up in your body and cause side effects (called “metabolic acidosis”).

Warnings and Precautions

1. What is hexatrione, with what you need to know before using HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)?

2. IN ALL CASES, STRICTLY COMPLY WITH THE MEDICAL PRESCRIPTION

Method and route of administration

1. Hexatrione contains a potent glucocorticoid and should be used with caution when the condition justifies a strong local concentration.

2. If the injections are multiple, due to the risk of accumulation and toxicity (metabolic acidosis).

3. Interactions with other drugs and other forms of interactions

4. Possible side effects of using hexatrione, with what you need to know before using HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)?
5.2 Pharmacokinetic properties

4.7 Effects on ability to drive and use machines

5. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

4.10 Special precautions for disposal and handling

5.2. Pharm acokinetic properties

4.1. Pharm acodynamic properties

5. PHARMACOLOGICAL PROPERTIES

4.8 Side effects

5. PHARMACOLOGICAL PROPERTIES

4.1. Pharm acodynamic properties

5.1. Pharm aceutical data

4.9. Overdose

5.1. Pharm acological properties

4.8. Side effects

5.1. Pharm acological properties

4.5. Unusual side effects due to overdosage

5.1. Pharm acological properties

4.3. Overdosage

5.2. Pharmacokinetic properties

4.4. Special precautions for storage

5.2. Pharmacokinetic properties

4.5. Unusual side effects due to overdosage

5.1. Pharm acological properties

4.6. Special precautions for disposal and handling

5.1. Pharm acological properties

4.8. Side effects

5.1. Pharm acological properties

4.7. Effects on ability to drive and use machines

5. PHARMACOLOGICAL PROPERTIES

4.8. Side effects
INSTRUCTIONS FOR OPENING ONE POINT CUT (OPC) AMPOULES

ONE POINT CUT (OPC) AMPOULES

The medicinal product is filled into pre-scored One Point Cut (OPC) ampoules. A colored dot on the bulbous part of the ampoule indicates the position of the score. OPC ampoules can be opened easily and safely, reducing the risk of splintering and/or sharp edges.

PREPARE YOUR WORK AREA

Medicinal products filled in glass ampoules must remain sterile. Therefore, clean the work area, disinfect your hands and the outside of the ampoules. The use of an ampoule holder may be helpful.

OPENING ONE POINT CUT (OPC) AMPOULES WITHOUT AMPOULE OPENER

- Pick up the ampoule and hold its lower part between your thumb and index finger. Make sure to remove all the liquid from the top of the ampoule by gently tapping it with a finger of the other hand. Hold the ampoule so that the colored dot faces you.
- Grasp the top of the ampoule with your other hand. Place your thumb onto the colored dot and the index finger on the opposite side (back) of the bulbous part of the ampoule.
- Hold the bottom of the ampoule firmly in an upright position and push the top section away from the colored dot with light, even pressure. The ampoule should break with a clean snap. Using too much force can cause the ampoule to shatter! If the ampoule shatters, discard it and use a new ampoule.
- If the ampoule does not break open, readjust its position in your hands and try again. If it seems extremely hard to open, do not try to open it by force. Try with a different ampoule or use an ampoule opener.
OPENING ONE POINT CUT (OPC) AMPOULES WITH AN AMPOULE OPENER

- Pick up the ampoule and hold its lower part between your thumb and index finger. Make sure to remove all the liquid from the top of the ampoule by gently tapping it with a finger of the other hand. Hold the ampoule so that the colored dot faces you.
- With your other hand, slip the ampoule opener over the top of the ampoule right into the neck below the bulbous part.
- Grasp the ampoule opener with your thumb and index finger placed on opposite sides on the indicated area close to the ampoule neck and make sure that the dot on the ampoule is still in position under your thumb.
- Hold the bottom of the ampoule firmly in an upright position and push the top section away from the colored dot with light, even pressure. The ampoule should break with a clean snap. Do not be surprised if the ampoule top jumps out of the opener when the ampoule snaps open.

SAFETY ASPECTS AND MISTAKES

- To prevent shattering of the glass, never try to break ampoules by force!
- Always apply pressure away from the colored dot, never in any other direction.
- Avoid any pushing, pulling, or twisting actions while applying pressure on the ampoule to open it.
- Pressure between the index finger and the thumb of either hand can cause the ampoule to break in an unintended manner and may cause injuries to the operator.
• If the ampoule does not break open, readjust its position in your hands and try again. If it seems extremely hard to open, do not try to open it by force. Try with a different ampoule or use an ampoule opener.
• Do not use the medicine if your ampoule shatters or if the opened ampoule is contaminated with glass after opening.

Experience is essential for a clean break when opening ampoules. Operators will find that they will develop their individual opening technique with time.