MEDEXUS PHARMA

June 14, 2022

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

ANDA SUITABILITY PETITION
TRIAMCINOLONE HEXACETONIDE INJECTABLE SUSPENSION, USP
40 mg/2 mL Vial (20 mg/mL)

Dear Sir / Madam,

The undersigned submits this petition under 21 CFR 10.20, 10.30 and 314.93 and Section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of the Food and Drugs to grant the Petitioner permission to file an Abbreviated New Drug Application (ANDA), 2 mL fill volume for Triamcinolone hexacetonide injectable suspension (20 mg/mL), USP in response to a current drug shortage as discussed below.

A. Action Requested

The petitioner requires that the Commissioner of the Food and Drug Administration declare that a 2 mL fill volume for Triamcinolone hexacetonide injectable suspension, USP (20 mg/mL), is acceptable for submission as an ANDA.

The previously approved and currently discontinued reference listed drug (RLD) upon which this petition is based, is the 1 mL fill for ARISTOSPAN® (triamcinolone hexacetonide injectable suspension, USP), 20 mg/mL vial, NDA 016466 held by Sandoz Inc.

ARISTOSPAN® was withdrawn from the commercial market approximately 6 years ago and the Petitioner has submitted a Citizen Petition formally requesting a Safety and Efficacy determination regarding the withdrawal of the subject drug product from the market, Docket number FDA-2022-P-1104.

The Petitioner is currently importing Hexatrione® (triamcinolone hexacetonide) injectable suspension, (20 mg/mL) in 2 mL filled glass ampoules with a total strength of 40 mg per ampoule via an FDA Drug Shortage import authorization, see DHCP Letter.

The applicant is requesting that the total vial content for this injectable suspension be increased from 1 mL to 2 mL; increasing the total strength per vial to 40 mg in support of an ANDA registration to address the current drug shortage. The concentration of the suspension remains unchanged as 20 mg/mL triamcinolone hexacetonide.

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B. Statement of Grounds

Section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic Act provides for the submission of an ANDA for a drug product that differs in strength (or in this case a parenteral drug product, total drug content) from that of the reference listed drug (RLD) provided the FDA has approved a petition that proposes filing such an application.

The proposed drug product represents an injectable dosage form at a concentration of 20 mg/mL but containing a total drug volume of 2 mL in the vial container. Historically, the Agency has required a firm to submit and obtain approval of a Suitability Petition prior to permitting a change in the total drug content in a parenteral drug product (i.e., the amount or total volume, in a single container, e.g. a vial), even though the concentration of the drug product remains exactly the same. The Agency has indicated that they consider this synonymous to a change in strength and this is the intent and purpose of this petition.

There are no proposed changes in labeling except for the obvious changes in strength (total drug content by volume) sought in this petition. The uses, indications, warnings, and directions for use will remain the same as that of the previously approved drug.

Therefore, the petitioner's request for the Agency to find that a change in strength (total drug content from 1 mL/vial to 2 mL / vial) should raise no questions of safety or effectiveness, and the Agency should approve the petition.

A comparison of the previously approved RLD formulation and the proposed Triamcinolone hexacetonide injectable suspension (20 mg/mL) drug product is provided below.

	Reference Listed Drug*	**Proposed Drug Product**
Name	Aristospan® Triamcinolone Hexacetonide Injectable suspension	Hexatrione® Triamcinolone Hexacetonide Injectable suspension
Non-proprietary name	Triamcinolone Hexacetonide	Triamcinolone Hexacetonide
Dosage form	Suspension	Suspension
Route of Administration	Intra-articular injection	Intra-articular injection
Indication	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.	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.
Strength/mL	20 mg/mL	20 mg/mL

	Reference Listed Drug*	Proposed Drug Product
Volume	1 mL	2 mL
Total strength	20 mg per vial	40 mg per vial
Formulation		
Active Ingredient	Triamcinolone hexacetonide 20 mg/mL	Triamcinolone hexacetonide 20 mg/mL
Viscosity Agent	Sorbitol 50.0% w/v	Sorbitol 50.0% w/v
Preservative	Benzyl alcohol 0.90% w/v	Benzyl alcohol 0.90% w/v
Wetting agent	Polysorbate 80 0.40% w/v	Polysorbate 80 0.40% w/v
pH adjuster	HCl or NaOH q.s. to pH 4.0- 8.0	HCl or NaOH q.s. to pH 4.0- 6.5
Vehicle	Water for injection q.s to 1 mL	Water for injection q.s to 1 mL

* Per the approved label for NDA 016466 ARISTOSPAN® (triamcinolone hexacetonide injectable suspension, USP), 20 mg/mL.

The proposed drug product is identical in indication, active ingredient, excipients, dosage form and route of administration as the listed drug, ARISTOSPAN® (triamcinolone hexacetonide injectable suspension, USP), 20 mg/mL, NDA 016466 held by Sandoz Inc., except for fill volume.

C. Environmental Impact

In Accordance with the requirements set forth in 21 CFR § 10.31 (a), the Petitioner hereby requests a Categorical Exclusion from the requirements of an environmental impact analysis.

D. Economic Impact Statement

Pursuant to 21 C.F.R. § 10.30(b), Petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis, if requested by the Agency.

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E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,

Khaled M Mohamed

Digitally signed by Khaled M Mohamed
Date: 2022.06.14 09:50:58 -05'00'

Khaled M Mohamed
Director, Regulatory Affairs
Medexus Pharma, Inc.
T: 312.854.0515
Email: khaled.mohamed@medexus.com

June 10, 2022

Khaled Mohamed
Medexus Pharma, Inc.
29 N. Wacker Drive, Suite 704
Chicago, IL 60606

Sent via email to: khaled.mohamed@medexus.com

Dear Petitioner:

Your submission requesting that the Commissioner of Food and Drug determine whether the Reference Listed Drug (RLD), ARISTOSPAN® (triamcinolone hexacetonide injectable suspension, USP), 20 mg/mL, NDA 016466 held by Sandoz Inc., has been voluntarily withdrawn from the commercial market or withdrawn from sale for safety or effectiveness reasons was received and processed under CFR 10.30 by this office on 06/09/2022.

It was assigned docket number FDA-2022-P-1104. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note, the acceptance of the petition for filing is a procedural matter and in no way reflects the Agency's decision on the substantive merits of the petition.

Sincerely,

Karen Malvin
Acting Director
Dockets Management Staff
FDA/Office of Operations (OO)

December 8, 2021

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 Aristospan® (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:

Product name and description	Size	Package	NDC
Hexatrione 2% Injectable Suspension (INTRA-ARTICULAR), 40 mg per ampoule (20 mg/ml)	2 mL ampoule	one ampoule per carton	59137-570-01

There are key differences between the labeling of the FDA approved Aristospan® (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, Aristospan®, 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.

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- 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

- **Regular Mail or Fax:** Download form 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

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Product Comparison Table

	US Approved Product	Imported Product
Product Name	Aristospan® (Triamcinolone Hexacetonide Injectable Suspension, USP)	Hexatrione 2% (triamcinolone hexacetonide), injectable suspension
Non-proprietary or Common Name of Drug Substance (Medicinal Ingredient)	Triamcinolone hexacetonide	Triamcinolone hexacetonide
Dosage Form(s)	Suspension	Suspension
Strength(s)	20 mg/mL	20 mg/mL
Formulation		
Triamcinolone hexacetonide	20 mg/mL	20 mg/mL
Sorbitol	50.0% w/v	50.0% v/v
Polysorbate 80	0.40% w/v	0.40% w/v
Benzyl alcohol	0.90% w/v	0.90% w/v
Water for injection	q.s. to 1 mL	q.s. to 1 mL
Container Closure System	2 mL glass vial	2 mL type I colorless glass free-breaking ampoule
Route of Administration	Intra-Articular	Intra-Articular
Indications and Usage	The intra-articular or soft tissue administration of Aristospan® 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 intra-articular or soft tissue administration of Hexatrione 2% is indicated in rheumatological conditions by intra-articular injections: inflammatory arthritis (adult forms, juvenile idiopathic arthritis in infants aged at least one year, in children and adolescents), arthritis in flare.

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Description		Hexatrione 2% (triamcinolone hexacetonide), injectable suspension is a suspension of milky white appearance, with no apparent crystalline formation.
Dosage and Administration: **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.	Hexatrione 2% should not be diluted before injection.
Storage Conditions	Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. Protect from light. **DO NOT FREEZE.**	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
How Supplied	NDC 0781-3085-71 1 mL fill in 2 mL Vial	NDC 59137-570-01 2 mL Ampoule

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Primary Container Label	 NDC 0781-3085-71 **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 Lot: Exp.: 100744 F P O (01)00000000000000	**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 Ethypharm L100233 Lot: DMA86 Exp: 03-2023

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	NDC 0781-3085-75 **Aristospan®** **(triamcinolone hexacetonide injectable suspension, USP)** **100 mg/5 mL** Sterile (20 mg/mL) FOR INTRA-ARTICULAR USE. NOT FOR INTRAVENOUS USE. SHAKE WELL. ℞ 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 4.0-8.0. Preservative: Benzyl alcohol 0.90%. Store at 20°-25°C (68°-77°F) (see USP Controlled Room Temperature). **DO NOT FREEZE. PROTECT FROM LIGHT. SHAKE WELL.** 07-2008M Manufactured in Canada by Sandoz Canada Inc. for Sandoz Inc., Princeton, NJ 08540 1006747 (01)00000000000000 E.P.D. Lot: Exp.:	
Carton Primary Panel	NDC 0781-3085-71 **Aristospan®** **(triamcinolone hexacetonide injectable suspension, USP)** **20 mg/mL** FOR INTRA-ARTICULAR USE NOT FOR INTRAVENOUS USE SHAKE WELL Sterile ℞ only 1 mL Vial SANDOZ NDC 0781-3085-75 **Aristospan®** **(triamcinolone hexacetonide injectable suspension, USP)** **100 mg/5 mL** (20 mg/mL) FOR INTRA-ARTICULAR USE NOT FOR INTRAVENOUS USE SHAKE WELL STERILE ℞ only 5 mL Vial SANDOZ	LOT: DMA86 EXP: 03-2023 HEXATRIONE® 2% Triamcinolone Hexacetonide Injectable Suspension (INTRA-ARTICULAR) 20 mg/mL This carton contains one 2ml ampoule FOR INTRA-ARTICULAR USE ONLY NOT FOR INTRAVENOUS USE SHAKE WELL Sterile RX only See full prescribing information for dosage and administration Manufactured for: Medexus Pharma Inc. Chicago, IL 60606 USA Manufactured by: Laboratoires ETHYPHARM, Saint-Cloud, France NDC 59137-570-01 MEDEXUS PHARMA CTN 10036 HEXATRIONE® 2% Triamcinolone Hexacetonide Injectable Suspension (INTRA-ARTICULAR) ONLY FOR INTRA-ARTICULAR ADMINISTRATION 2ML AMPOULE MEDEXUS PHARMA HEXATRIONE® 2% Triamcinolone Hexacetonide Injectable Suspension (INTRA-ARTICULAR) 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 Benzyl Alcohol as a Preservative Store below 30°C (86°F) Protect from light. 3400931841302	

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Carton Composition Panel	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: Benzyl 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 Benzyl Alcohol as a Preservative

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Aristospan®
(Triamcinolone Hexacetonide Injectable Suspension, USP)
20 mg/mL PARENTERAL

NOT FOR USE IN NEWBORNS

FOR INTRA-ARTICULAR USE

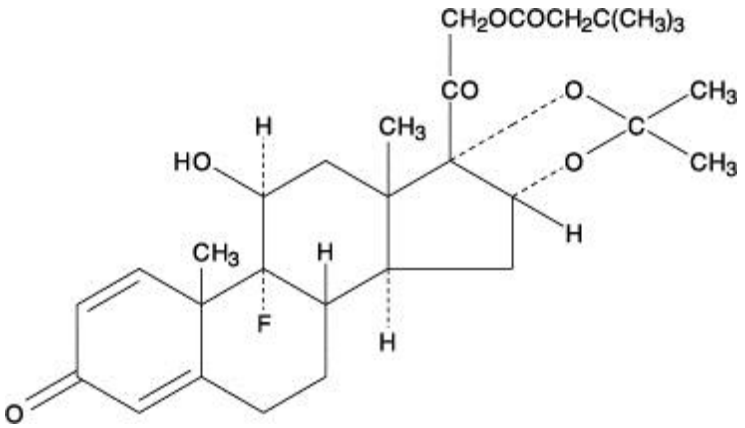
NOT FOR INTRAVENOUS USE

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 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:



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 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 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/m^2bsa/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 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

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

ANSM - Updated on: 24/09/2019

Name of the drug

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

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 WHAT IT IS USED FOR?

Pharmacotherapeutic group: GLUCOCORTICOIDE - ATC code: H02AB08

This medication is a corticosteroid.

It is used by intra-articular injection in rheumatology in inflammatory arthritis (adult forms, juvenile idiopathic arthritis in infants aged at least 1 year, in children and adolescents), and in relapsing osteoarthritis.

2. WHAT YOU NEED TO KNOW BEFORE USING HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)?

Never use HEXATRIONE 2 PERCENT, suspension for injection (intra-articular):

- In case of local or general infection or suspected infection,
- If you are allergic to triamcinolone or any of the other ingredients of this medicine listed in section 6.
- In case of coagulation disorders,
- If injected through intradiscal
- If injected into soft tissue (tendons, enthesitis)
- In neonates (up to 4 weeks) unless your doctor recommends otherwise, due to the presence of benzyl alcohol
- For more than a week in young children (under 3 years), unless your doctor or pharmacist.

Warnings and Precautions

Talk to your doctor or pharmacist before using HEXATRIONE 2 PERCENT, suspension for injection (intra-articular).

Take special care with HEXATRIONE 2 PERCENT, suspension for injection (intra-articular):

Special warnings

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.

Corticosteroid therapy can promote the occurrence of various infectious complications. Therefore, before treatment, you should tell your doctor in case of recent vaccination and evolving viral diseases (viral hepatitis, herpes, chickenpox, shingles), or if pain or fever appears after the injection.

Repeated injections may cause clinical and biological symptoms of hypercorticism (weight gain, swelling, hypertension, etc.) and unbalance diabetes, mental disorders or severe arterial hypertension.

The local injection of corticosteroids should be cautious during concomitant anticoagulant therapy.

Oral or injectable corticosteroids can promote the appearance of tendinopathy, or even tendon rupture (exceptional). Tell your doctor if you have tendon pain.

This medicine contains 9 mg of benzyl alcohol per ml of suspension for injection.

Benzyl alcohol can cause allergic reactions.

Benzyl alcohol is associated with a risk of serious side effects including breathing problems (called "suffocation syndrome") in young children.

Ask your doctor or pharmacist for advice if 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").

Precautions for use

This medication should not be injected into soft tissues (tendons, entheses).

Children

Not applicable.

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

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

HEXATRIONE 2 PERCENT, suspension for injection (intra-articular) with food and drink

Not applicable.

Pregnancy and breast feeding

This medication can be taken occasionally during pregnancy or breastfeeding, if needed.

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 before taking this medicine. Sportsmen

This specialty contains an active ingredient that can induce a positive reaction to the tests performed during doping controls.

Driving and using machines

Not applicable.

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

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

Dosage

Adult: The dosage varies from 0.5 to 2 ml of suspension depending on the size of the joint, i.e. 10 to 40 mg of triamcinolone hexatrione, without exceeding two 40 mg ampoules.

Children: The usual recommended dose is 5 mg (0.25 ml) to 40 mg (2 ml) by injection. Do not exceed 40 mg per injection.

Follow your doctor's prescription.

IN ALL CASES, STRICTLY COMPLY WITH THE MEDICAL PRESCRIPTION

Method and route of administration

STRICT INTRA-ARTICULAR ROUTE

Frequency of administration

Follow your doctor's prescription.

Duration of treatment

It is determined by your doctor.

HEXATRIONE 2 PERCENT, suspension for injection (intra-articular) - Summary of product characteristics

ANSM - Updated on: 24/09/2019

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Triamcinolone hexacetonide ..... 2,000 g

For 100 ml of suspension for injection.

Excipient with known effect: benzyl alcohol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This product contains a potent glucocortoid and should be used with caution when the condition justifies a strong local concentration. Prior to local injection, consider risk of infections, in particular the risk of promoting bacterial proliferation.

This product is indicated in rheumatological conditions by intra-articular injections: inflammatory arthritis (adult forms, juvenile idiopathic arthritis in children and adolescents), acute forms of inflammatory arthritis.

4.2. Posology and method of administration

Dosage

STRICT INTRA-ARTICULAR ROUTE

Anti-inflammatory equivalence (equipotence) for 5 mg of prednisone = 4 mg of triamcinolone.

Adult: 0.5 to 2 ml of suspension depending on the size of the joint, i.e. 10 to 40 mg of triamcinolone hexacetonide, without exceeding two 40 mg ampoules. Superficial injection should be avoided because of the risk of skin atrophy.

The injection will only be repeated if the symptoms recur or persist.

Infants (> 1 year), children and adolescents: administration is reserved for practitioners with experience in the treatment of the pathology.

The dose will be adjusted according to the size of the joint in order to avoid any reflux that could lead to periarticular calcifications and skin atrophy. The usual recommended dose is 5 mg (0.25 ml) to 40 mg (2 ml) per injection. Do not exceed the dose of 40 mg per injection.

The injection will only be repeated if symptoms reappear or persist, after a minimum of 3 to 6 months compared to the previous administration.

Shake the ampoule before use.

This formulation is not suitable for administration by inhalation by nebulizer.

4.3. Contraindications

This medication is contraindicated in the following situations:

- Local or general infection, or suspected infection,
- Severe coagulation disorders,
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- Intrathecal administration,
- Injection in soft tissue (synovial tendon sheaths, entheses).

4.4. Special warnings and precautions for use

The benefit / risk ratio should be carefully evaluated before any administration of HEXATRIONE in children under 3 years of age, taking into account the presence of benzyl alcohol which may 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)
- Psychotic states still not controlled by treatment,
- Live 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.

The local injection of corticosteroids should be performed with caution during concomitant anticoagulant therapy.

Oral or injectable corticosteroids can promote the appearance of tendinopathy, or even tendon rupture (exceptional). This risk is increased when co-prescribed with fluoroquinolones and in dialysis patients with secondary hyperparathyroidism or who have undergone kidney transplantation.

Attention is drawn to athletes, this formulation contains an active drug substance that may result in a positive test during anti-doping drug testing.

Strict aseptic administration technique is necessary.

The local injection of corticosteroids can negatively impact control of diabetes, a psychotic state, severe arterial hypertension.

This medicine contains 9 mg of benzyl alcohol per ml of suspension for injection.

Benzyl alcohol can cause allergic reactions.

Benzyl alcohol has been associated with a fatal "Gasping Syndrome" in premature infants and infants of low birth weight. Intravenous administration of benzyl alcohol has been associated with serious side effects and death in newborns ("suffocation syndrome"). The minimum amount of benzyl alcohol that can cause toxicity is not known. In addition, given the increased risk of accumulation in young children (under 3 years), it should not be used for more than a week.

High volumes should be used with caution and when clearly needed, especially in people with hepatic or renal impairment due to the risk of accumulation and toxicity (metabolic acidosis).

4.5. Interactions with other drugs and other forms of interactions

Please tell your doctor if you are taking, have recently taken or might take any other medicines, including over the counter medication. Some medicines may increase the effects of glucocorticoids and your doctor may wish to monitor you carefully. These risks should be considered in the event of multiple injections (several locations) or repeated in the short term.

Associations to take into account

+ Fluoroquinolones

Possible increased risk of tendinopathy, or even tendon rupture (rarely), particularly in patients receiving prolonged corticosteroid therapy.

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal teratogenesis studies have not been performed with topical corticosteroids.

However, studies on *oral* corticosteroid intake in pregnant women have not revealed a higher risk of malformation than that observed in the general population.

Therefore, this medication can be prescribed during pregnancy if needed.

However, this medicine contains benzyl alcohol. In pregnant women, there is a risk of accumulation of benzyl alcohol which can lead to metabolic acidosis.

Feeding with milk

Breast-feeding is possible while taking this medicine.

However, the risk of systemic corticosteroids should be considered in the event of multiple injections (several locations) or repeated short-term (see section 4.4).

This medicine contains benzyl alcohol. In lactating women, there is a risk of accumulation of benzyl alcohol which may lead to metabolic acidosis.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Side effects

Systemic side effects of glucocorticoids have a low risk of occurring after topical administration due to low blood levels. But the risk of hypercortisolism (fluid retention, imbalance of diabetes and arterial hypertension ...) increases with the dose and frequency of injections:

- Risk of local infection (depending on the injection site): arthritis,
- Localized atrophy of muscle tissue, subcutaneous and skin. Risk of tendon rupture if injected into the tendons,
- A few cases of tendon ruptures have been described exceptionally, in particular in co-prescription with fluoroquinolones.
- Acute arthritis in microcrystals (with microcrystalline suspension) early onset,
- Local calcification,
- Local and systemic allergic reactions,
- Flush: headache and flushing may occur. They usually go away in a day or two.

The safety profile in children is similar to that reported in adults.

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions after authorization of the drug is important. It allows continuous monitoring of the benefit / risk ratio of the medicinal product. Healthcare professionals report any suspected adverse reactions via the national reporting system: National Agency for Medicines and Health Products Safety (ANSM) and network of Regional Pharmacovigilance Centers - Website: www.signalement-sante.gouv.fr.

4.9. Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB08 (H: non-sex hormones).

Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticosteroids, including this formulation, are used primarily for their anti-inflammatory effect.

In high doses, they decrease the immune response. Their metabolic and sodium retention effect is less than that of hydrocortisone.

Intra-articular injection of triamcinolone hexacetonide is characterized by a prolonged duration of action.

5.2. Pharmacokinetic properties

After intra-articular injection, resorption of triamcinolone hexacetonide is slow, complete after only 2 to 3 weeks. If the conditions of use are followed (see section 4.2), the risk of systemic absorption is very low.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Benzyl alcohol, polysorbate 80, sorbitol at 70 p. 100 (crystallizable), dilute hydrochloric acid or sodium hydroxide, water for injections.

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. The duration of the expiration

3 years

After opening: the product should be used immediately.

6.4. Special precautions for storage

Store at a temperature below 30°C and protected from light.

6.5. Nature and contents of the outer packaging

1 ml or 2 ml type I colorless glass free-breaking ampoule.

6.6. Special precautions for disposal and handling

Shake before use.

7. MARKETING AUTHORIZATION HOLDER

ETHYPHARM LABORATORIES
179 HILL OFFICES
92210 SAINT-CLOUD

8. MARKETING AUTHORIZATION NUMBER (S)

- 34009 318 412 1 4: 1 ml ampoule (colorless glass).
- 34009 318 413 0 2: 2 ml ampoule (colorless glass).

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

[to be completed later by the holder]

10. DATE OF UPDATE OF THE TEXT

[to be completed later by the holder]

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICS

Not applicable.

PRESCRIPTION AND DELIVERY CONDITIONS

List I

If you use more HEXATRIONE 2 PERCENT, suspension for injection (intra-articular) than you should

Not applicable.

If you forget to use HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)

Not applicable.

If you stop using HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)

Not applicable.

4. WHAT ARE THE POSSIBLE SIDE EFFECTS?

Like all medicines, this medicine can cause side effects, although not everybody gets them.

- Local risks: infection, inflammation or calcification of the joint,
- A few cases of tendon ruptures have been described exceptionally, in particular as a co-prescription with fluoroquinolones,
- Headaches and flushing may occur. They usually go away within a day or two,
- Weakening of the skin,
- Repeated injections may result in symptoms of hyperadrenocorticism (weight gain, swelling) and disrupt diabetes, hypertension,
- Local and general allergic reactions.

Reporting of side effects

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. You can also report side effects directly via the national reporting system: National Agency for Medicines and Health Products Safety (ANSM) and network of Regional Pharmacovigilance Centers - Website: www.signalement-sante.gouv.fr

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE HEXATRIONE 2 PERCENT, suspension for injection (intra-articular)?

Keep this medication out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiration date refers to the last day of that month.

After opening: the product should be used immediately.

Store at a temperature below 30°C and protected from light.

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACKAGE AND OTHER INFORMATION

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

- The active substance is:

Triamcinolone hexacetonide ..... 2.0 g

For 100 ml.

- The other ingredients are:

Benzyl alcohol, polysorbate 80, sorbitol at 70 p. 100 (crystallizable), dilute hydrochloric acid or sodium hydroxide, water for injections.

What is HEXATRIONE 2 PERCENT, suspension for injection (intra-articular) and contents of the pack

Suspension for injection in 1 ml or 2 ml ampoule

Marketing authorization holder

ETHYPHARM LABORATORIES
179 HILL OFFICES
92210 SAINT-CLOUD

Marketing authorization operator

ETHYPHARM LABORATORIES
179 HILL OFFICES
92210 SAINT-CLOUD

Maker

VALDEPHARM
INCARVILLE INDUSTRIAL PARK
27100 VAL DE REUIL
FRANCE

Names of the drug in the Member States of the European Economic Area

Not applicable.

The last date on which this leaflet was revised is:

[to be completed later by the holder]

Other

Detailed information on this medication is available on the ANSM website (France).

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.

Aristospan®
(Triamcinolone Hexacetonide Injectable Suspension, USP)
20 mg/mL PARENTERAL

NOT FOR USE IN NEWBORNS

FOR INTRA-ARTICULAR USE

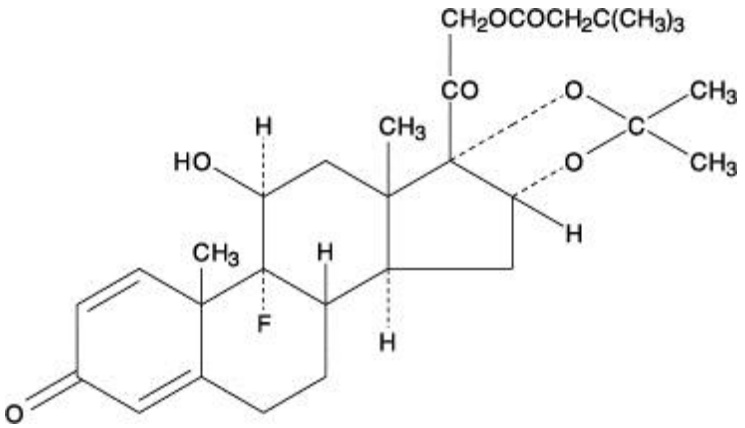
NOT FOR INTRAVENOUS USE

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 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:



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 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 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/m^2bsa/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 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

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Manufactured in Canada by

Sandoz Canada Inc. for

Sandoz Inc., Princeton, NJ 08540