

**COMPLETE PRESCRIBING INFORMATION**

**ARISTOSPAN SUSPENSION  
Triamcinolone Hexacetonide**

**(Glucocorticoid)**

**Adrenocorticoid**

©

**VALEO PHARMA INC.  
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**ARISTOSPAN SUSPENSION**

**THERAPEUTIC CLASSIFICATION**

Adrenocorticoid

**CHEMISTRY**

**Molecular Formula:**  $C_{30}H_{41}FO_7$     **Molecular Weight:** 532.66

**Chemical Name:**            9 $\alpha$ -Fluoro-11 $\beta$ , 21-dihydroxy-16 $\alpha$ , 17 $\alpha$ -(isopropylidenedioxy)-1, 4-pregnadiene-3, 20-dione, 21-(3, 3-dimethylbutyrate).

**Description:**                Triamcinolone hexacetonide is a white or cream coloured powder, insoluble in water.

### ACTION

Naturally occurring glucocorticoids, which also have salt-retaining properties, are used as replacement therapy in adrenal-cortical deficiency states. Their synthetic analogs are primarily employed for their potent anti-inflammatory effects in disorders of many body organs. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

ARISTOSPAN is not rapidly removed from the site of injection after intra-articular administration, nor is it rapidly metabolized in situ.

### INDICATIONS AND CLINICAL USES

#### Intra-articular

ARISTOSPAN is indicated for treatment of synovitis of osteoarthritis, acute and subacute bursitis, epicondylitis, post-traumatic osteoarthritis, rheumatoid arthritis, acute gouty arthritis, acute non-specific tenosynovitis.

Since ARISTOSPAN has low solubility, if a more immediate therapeutic effect is desired, then a more soluble corticosteroid should be administered locally or systemically.

### CONTRAINDICATIONS

ARISTOSPAN should not be used when systemic fungal infection is present.

### **WARNINGS**

1. **ARISTOSPAN should not be given intravenously.**
2. **Active, latent or questionably healed tuberculosis, ocular herpes simplex and acute psychosis are considered to be conditions which require caution when glucocorticoid therapy is utilized.**
3. **In pregnancy, particularly during the first trimester, steroids should be considered only when the benefits outweigh the risks involved, since fetal abnormalities have been observed in experimental animals.**
4. **Steroids should be used with caution in cases of psychic disturbances, in acute glomerulonephritis, active or latent peptic ulcer, myasthenia gravis, osteoporosis, fresh intestinal anastomoses, diverticulitis, thrombophlebitis, diabetes mellitus, hyperthyroidism, acute coronary artery disease, hypertension, limited cardiac reserve or systemic infections including exanthematous diseases.**
5. **Caution regarding vaccination against smallpox and other immunization procedures is advised.**
6. **Ophthalmic complications during prolonged corticosteroid therapy have been observed. These include posterior subcapsular cataract, glaucoma and possible damage to optic nerves and enhancement of secondary ocular infections due to fungi or virus.**

7. Calcium excretion is increased during corticosteroid therapy.
8. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.
9. Appropriate examination of any joint fluid present is necessary to avoid a septic process.

#### **PRECAUTIONS**

##### **General**

Precautions common to all corticosteroid therapy should be observed:

1. If severe reactions, anaphylactoid reactions or idiosyncrasies occur, therapy should be discontinued and appropriate measures instituted.
2. Since corticosteroids depress adrenocortical function, therapy should be withdrawn gradually after prolonged treatment.
3. When patients on ARISTOSPAN for up to one (sometimes two) years after discontinuation are subjected to unusual stress (trauma, surgery), administration of a soluble corticosteroid should be considered.
4. Corticosteroid therapy may obscure symptoms of developing infectious disease. If infection occurs, appropriate antimicrobial measures should be taken.

5. Growth suppression of children is possible during prolonged therapy.
6. Corticosteroid therapy provides symptomatic treatment and does not obviate the need for conventional measures.
7. Infants of mothers who have received adrenocortical hormones during pregnancy should be observed closely for signs of hypoadrenalism and corrective hormone therapy instituted if such signs are evident. Since spontaneous remission of some diseases, such as rheumatoid arthritis, may occur during pregnancy, effort should be made to avoid corticosteroid therapy during pregnancy.
8. Corticosteroids may suppress reactions to skin tests.
9. ASA should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.
10. There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

**Intra-articular Use**

The prolonged and repeated use of glucocorticoids in weight bearing joints may result in further joint degeneration. This may be related to increased use of still-diseased joints following relief of pain and other symptoms, or it may be due to inhibition by corticosteroid

of protein synthesis in articular cartilage. It is inadvisable to inject unstable joints; repeated injections may, in some cases, result in instability of the joint.

Inadvertent injection into the soft tissues around the joint may lead to an increased incidence of systemic effect. As with all intra-articular injections, care should be taken to avoid entering a blood vessel.

A marked increase in pain, accompanied by local swelling, further restriction of joint motion, fever and malaise occurring after intra-articular injection is suggestive of septic arthritis. If this complication appears and the diagnosis of sepsis is confirmed, antimicrobial therapy should be instituted immediately and continued for at least seven to ten days after clinical evidence of infection has disappeared.

Over-distention of the joint capsule and deposition of the steroid along the needle track should be avoided.

Patients should be advised not to overuse treated joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active.

#### **ADVERSE REACTIONS**

##### **Intra-Articular**

As with all glucocorticoids, an exacerbation of symptoms or "flare-up" may occur following injection. Local atrophy, burning, flushing, pain and swelling may occur.

Charcot-like arthropathy may occur.

Temporary blindness associated with therapy around the face and head have been reported following the intralesional administration of corticosteroids, particularly around the eyes and nose.

**Systemic Effects**

Systemic effects have occurred infrequently with ARISTOSPAN (triamcinolone hexacetonide), but, nevertheless, the physician should observe the patient for the following:

**Specific Triamcinolone Effects:**

Certain systemic effects may occur that do not occur or may occur less frequently with other corticosteroids. These include:

1. A depression of appetite, in contrast to voracious appetite ordinarily encountered with other glucocorticoids.
2. Most common corticosteroids may cause euphoria whereas triamcinolone may cause a mood depression.
3. Common glucocorticoids cause sodium retention and edema, but triamcinolone may produce a mild early diuresis, making edema uncommon.

4. A myopathy with muscle weakness involving the muscles of the thighs, pelvis and lower back may occur more frequently with triamcinolone than with other corticosteroids.

General Glucocorticoid Effects:

ARISTOSPAN may produce adverse effects common to all glucocorticoids: Cushingoid changes such as acne, flushing, moon face, hirsutism, etc.; endocrinologic effects such as amenorrhea, menstrual irregularity, aggravation of pre-existing diabetes mellitus and/or precipitation of latent diabetes mellitus; skeletal changes such as osteoporosis, spontaneous fractures, aseptic necrosis of the hip, humerus and metacarpals; psychic disturbances, insomnia, headache, increased intracranial pressure with papilledema (pseudotumor cerebri), convulsions; exophthalmos, increased intraocular tension, subcapsular cataracts, peptic ulcer with possible perforation and hemorrhage; ulcerative esophagitis; thromboembolic disease, ecchymoses, purpura, leukopenia, negative nitrogen balance; hypertension, and rarely, necrotizing angiitis and acute pancreatitis. the occurrence of these systemic effects is unlikely when ARISTOSPAN is used as recommended.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no satisfactory treatment or antidote known.

PHARMACOLOGY

ARISTOSPAN is a potent glucocorticoid, possessing the anti-inflammatory corticotropin suppressing, protein-catabolic and carbohydrate-storing activities characteristic of that class of drug.

The pharmacological action of triamcinolone hexacetonide has been shown to be less intense and more prolonged, but qualitatively the same as triamcinolone acetonide. It has been determined that the activity of triamcinolone hexacetonide is ascribable to the slow release of triamcinolone acetonide through hydrolysis. Following this reaction, the pharmacology is identical to that of the parent compound, triamcinolone acetonide.

### **TOXICOLOGY**

#### **Acute Studies**

The median lethal dose in mice after 7, 24 and 21 days was in excess of 4000 mg/kg, 2000 mg/kg and 1000 mg/kg respectively following subcutaneous administration. The median lethal dose in rats after 7 and 14 days was 119 mg/kg and 21 mg/kg, following subcutaneous administration.

#### **Subacute Studies**

Studies in the guinea pig: Intra-dermal administration of 1 ml (5 mg) of ARISTOSPAN (5 mg/ml) twice weekly for one month has shown no clinical signs of toxicity. Pathological changes at the site of injection were of comparable incidence and severity for both the drug treated and vehicle control group.

Studies in the dog: Intra-articular administration of 0.5 ml (10 mg) of ARISTOSPAN (20 mg/ml) twice weekly for one month has shown no adverse reactions in any animal which could be attributed to the repeated intra-articular administration of ARISTOSPAN or vehicle.

### Chronic Studies

Studies in the dog: After preliminary experiments involving intra-articular injections (15-19 injections) over a 13 week period at a dose of 1.6 mg/kg, no signs of joint deterioration were seen. Subsequently, another group received weekly intra-articular injections into the right stifle joint or weekly subcutaneous injections into an area above the dorsal thorax in doses of 0.4 and 1.6 mg/kg for 6 months. The doses 0.4 and 1.6 mg/kg are approximately equal to and four times the recommended therapeutic human intra-articular dose, respectively; the weekly dosing interval is three to four times the recommended therapeutic frequency.

The results showed that multiple intra-articular and subcutaneous injections of ARISTOSPAN were well tolerated. No signs of pain or discomfort were observed. The magnitude of the decrease in serum cortisol in response to ARISTOSPAN following intra-articular and subcutaneous doses was comparable to equivalent administration of ACTH (adrenocorticotrophic hormone).

After 22 to 25 doses, one of six dogs receiving 0.4 mg/kg/week and 4 of 6 dogs receiving 1.6 mg/kg/week of ARISTOSPAN exhibited signs of apparent joint deterioration. Radiographs of the stifle joint taken after 15 weeks of dosing in the 6 months study showed no changes in the stifle joints.

Hypertrophy, degeneration and necrosis of the synovial membranes, accompanied by subacute inflammation and erosion of the cartilaginous articular surfaces were seen in the stifle joints of all animals which received weekly intra-articular doses of 1.6 mg/kg and in

two of six animals which received weekly intra-articular injections of 0.4 mg/kg of ARISTOSPAN for six months.

Morphologic examination of the injection sites of animals which received subcutaneous doses of ARISTOSPAN or vehicle for six months revealed slight reddening of the skin, thickening of tissue, small palpable nodules, foci of subcutaneous necrosis and dystrophic mineralization.

The clinical findings in this study (apparent changes in the integrity of the stifle joint, eosinopenia and decrease in serum cortisol) were minimal in comparison to the usual signs which characterize glucocorticoid toxicity.

**Teratology Studies:**

Teratologic studies in rats and rabbits revealed maternal and fetal responses considered characteristic of the action of fluorinated corticosteroids in pregnant animals of these species.

Although the teratogenic effects of steroidal anti-inflammatory agents in laboratory animals are well known, these drugs are evaluated to have little or no teratogenic potential in man.

Extensive use of corticosteroids during human pregnancy has not been associated with the birth of defective children either in reported cases or in epidemiologic surveys.

### **DOSAGE AND ADMINISTRATION**

Strict aseptic administration technique is mandatory. Topical ethyl chloride spray may be used locally before injection. The vial should be gently agitated to achieve uniform suspension before each use. Since ARISTOSPAN Suspension has been designed for ease of administration, a small bore needle (25 to 26 gauge) may be used.

#### **Intra-Articular**

Average dose: 2 to 20 mg (0.1 ml to 1.0 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 injections 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 avoid deposition of drug along the needle path, which might produce atrophy.

## **AVAILABILITY**

How supplied: 1 ml/vial, 5 ml/vial and 1 ml (in a 2 ml LEDERJECT Disposable Syringe)

**DIRECTIONS FOR USE OF THE NEEDLELESS LEDERJECT DISPOSABLE SYRINGE. TO PREVENT LEAKAGE, USE ONLY WITH PLASTIC HUB DISPOSABLE SYRINGE NEEDLES.**

1. Grasp the rubber tip cap at its flange, twist and pull to remove.
2. Twist the plunger rod clockwise, and at the same time use a slight withdrawal pressure to loosen the rubber stopper.
3. Pull back the plunger rod slowly and carefully to ensure smooth plunger operation.
4. (a) Attach desired needle and expel the air bubble, or  
(b) expel the air bubble and attach to needle already in tissue.

## REFERENCES

1. Astorga, G.P.: Intra-Articular Use of Triamcinolone Hexacetonide, Arthritis Rheum., 11:813 (1968).
2. Bilka, P.J.: A New Long-Acting, Intra-Articular Steroid, Arthritis Rheum., 9:847 (1966).
3. Bilka, P.J.: A New Intra-Articular Steroid, Minnesota Medicine, 50:483-486 (1967).
4. Cassidy, J.T., and Bole, G.G.: Cutaneous Atrophy Secondary to Intra-Articular Corticosteroid Administration, Ann. Intern. Med., 65: 1008-1018 (1966).
5. Chandler, G.N., Jones, D.T., Wright, V., and Hartfall, S.J.: Charcot's Arthropathy Following Intra-Articular Hydrocortisone, Brit. Med. J. 1:952-953 (1959).
6. Clemmensen, S.: Triamcinolone Hexacetonide for Intra-Articular and Intra-Muscular Therapy, Acta Rheum. Scand. 17:273-278 (1971).
7. Dordick, J.R., and Bernstein, Z.L.: Intra-Articular Administration of Triamcinolone - Preliminary Report. New York J. Med. 59:3393-3397 (1959).
8. Hollander, J.H., Jessar, R.A., Restifo, R.A., and Fort, H.J.: A New Intra-Articular Steroid Ester with Longer Effectiveness, Arthritis Rheum. 4:422 (1961).
9. St. John Dixon, A., Cosh, J.A., and Kersley, George D.: Local Corticosteroid Therapy for Painful Rheumatic States, Clinical Trials Journal (London), 2:14-18 (1972).
10. Wilson, J.G.: Present Status of Drugs as Teratogens in Man, Teratology, 7:3-16 (1973).