

**PRODUCT MONOGRAPH**

**DEPO-MEDROL\* WITH LIDOCAINE**

(sterile methylprednisolone acetate suspension USP)

40 mg/mL

and

(lidocaine hydrochloride USP)

10 mg/mL

**Glucocorticoid with local anaesthetic**

Pfizer Canada Inc.  
17,300 Trans-Canada Highway  
Kirkland, Quebec, H9J 2M5

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**(sterile methylprednisolone acetate suspension USP with lidocaine hydrochloride)**

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**ACTION AND CLINICAL PHARMACOLOGY**

Methylprednisolone is an anti-inflammatory steroid. Estimates of the relative potencies of methylprednisolone and prednisolone range from 1.13 to 2.1 with an average of 1.5. In general the required daily dose of methylprednisolone can be estimated to be two-thirds (or 0.7) the required daily dose of prednisolone. While the effect of parenterally administered methylprednisolone acetate is prolonged, it has the same metabolic and anti-inflammatory actions as orally administered drug.

Cortisol and its synthetic analogues, such as methylprednisolone acetate, exert their action locally by preventing or suppressing the development of local heat, redness, swelling and tenderness by which inflammation is recognized at the gross level of observation. At the microscopic level, such compounds inhibit not only the early phenomena of the inflammatory process (edema, fibrin deposition, capillary dilatation, migration of phagocytes into the inflamed area and phagocytic activity), but also the later manifestations (capillary proliferation, fibroblast proliferation, deposition of collagen and still later cicatrization). These compounds inhibit inflammatory response whether the inciting agent is mechanical, chemical or immunological.

Lidocaine is a potent local anesthetic agent widely used both for topical and injection anaesthesia.

Lidocaine prevents both the generation and the conduction of the nerve impulse. Its main site of action is the cell membrane, and there is seemingly little action of physiological importance on the axoplasm. The exact mechanism whereby a local anesthetic influences the permeability of the membrane is unknown.

As a general rule, small nerve fibers are more susceptible to the action of local anaesthetics than are large fibers.

## **INDICATIONS AND CLINICAL USE**

### **FOR INTRA-SYNOVIAL OR SOFT TISSUE ADMINISTRATION**

(including periarticular and intrabursal) SEE WARNINGS

DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride) is indicated as adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: synovitis of osteoarthritis, rheumatoid arthritis, acute and subacute bursitis, acute gouty arthritis, epicondylitis, acute nonspecific tenosynovitis, post-traumatic osteoarthritis.

DEPO-MEDROL with Lidocaine may also be useful in cystic tumors of an aponeurosis or tendon (ganglia).

## **CONTRAINDICATIONS**

NOT FOR INTRAVENOUS USE

NOT FOR INTRATHECAL ADMINISTRATION

DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride) is contraindicated in systemic fungal infections and patients with known hypersensitivity to components of DEPO-MEDROL, Lidocaine or other local anesthetics of the amide type.

## WARNINGS

This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.

Multidose use of DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride) from a single vial requires special care to avoid contamination. Although initially sterile, any multidose use of vials may lead to contamination unless strict aseptic technique is observed. Particular care, such as use of disposable sterile syringes and needles is necessary.

While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physicochemical changes in the ground substance of the connective tissue. The resultant infrequently occurring dermal and/or subdermal changes may form depressions in the skin at the injection site.

The degree to which this reaction occurs will vary with the amount of adrenal steroid injected. Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed.

In order to minimize the incidence of dermal and subdermal atrophy, care must be exercised not to exceed recommended doses in injections. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intra-articular injection should include precautions against injection or leakage into the dermis.

DEPO-MEDROL with Lidocaine should not be administered by any route other than those listed under INDICATIONS. It is critical that, during administration of DEPO-MEDROL with Lidocaine appropriate technique be used and care taken to assure proper placement of drug.

Administration by other than indicated routes has been associated with reports of serious medical events including: arachnoiditis, meningitis, paraparesis/paraplegia, sensory disturbances, bowel/bladder dysfunction, seizures, visual impairment including blindness, ocular and periocular inflammation, and residue or slough at injection site. Appropriate measures must be taken to avoid intravascular injection.

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

Corticosteroids may mask some signs of infection, and new infections may appear during their use.

There may be decreased resistance and inability to localize infection when corticosteroids are used.

Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function.

These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Do not use intra-synovially, intrabursally, or for intratendinous administration for local effect in the presence of acute infection.

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

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

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patients have a history of allergy to any drug.

Allergic skin reactions have been reported apparently related to the excipients in the formulation (see DESCRIPTION). Rarely has skin testing demonstrated a reaction to methylprednisolone acetate, per se.

#### Usage in Pregnancy

Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. Adequate human reproductive studies have not been done with corticosteroids or with Lidocaine. Therefore the use of this drug in pregnancy, nursing mothers, or women of child bearing potential requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or fetus. Since there is inadequate evidence of safety in human pregnancy, this drug should be used in pregnancy only if clearly needed.

#### Labor and Delivery

Corticosteroids and lidocaine readily cross the placenta. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. There are no known effects of corticosteroids on labor and delivery. The use of local anesthetics such as lidocaine during labor and delivery may be associated with adverse effects on mother and fetus.

#### Nursing Mothers

Corticosteroids are excreted in breast milk. It is not known whether lidocaine is excreted in breast milk.

### Pediatric Use

Growth may be suppressed in children receiving long-term, daily-divided dose glucocorticoid therapy. The use of such a regimen should be restricted to those most serious indications.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids. However the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

### **PRECAUTIONS**

When multidose vials are used, special care to prevent contamination of the contents is essential. There is some evidence that benzalkonium chloride is not an adequate antiseptic for sterilizing multidose vials. A povidone-iodine solution or similar product is recommended to cleanse the vial top prior to aspiration of contents (See WARNINGS).

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

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.

Corticosteroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. Caution must also be used in diverticulitis,

fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis, when steroids are used as direct or adjunctive therapy.

The following additional precautions apply for parenteral corticosteroids:

Intra-synovial injection of a corticosteroid may produce systemic as well as local effects. No additional benefit derives from the intramuscular administration of DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride). Where parenteral corticosteroid therapy for sustained systemic effect is desired, plain DEPO-MEDROL should be used.

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

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

Local injection of a steroid into a previously infected joint is to be avoided.

Corticosteroids should not be injected into unstable joints.

Sterile technique is necessary to prevent infections or contamination.

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.

This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "gaspings syndrome" in premature infants.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

#### Carcinogenesis, mutagenesis, impairment of fertility

No evidence exists showing that corticosteroids are carcinogenic, mutagenic or impair fertility.

#### **Drug Interactions**

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and methylprednisolone, therefore it is possible that adverse events associated with the individual use of either drug may be more apt to occur.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of methylprednisolone and may require increase in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore the dose of methylprednisolone should be titrated to avoid steroid toxicity.

Methylprednisolone may increase the clearance of chronic high dose ASA. This could lead to a decrease in salicylate serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. ASA should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore coagulation indices should be monitored to maintain the desired anticoagulant effect.

## ADVERSE REACTIONS

### A. DEPO-MEDROL (methylprednisolone acetate)

**NOTE:** The following are typical for all systemic corticosteroids. Their inclusion in this list does not necessarily indicate the specific event has been observed with this particular formulation.

**Fluid and electrolyte disturbances** - Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

**Musculoskeletal** - Muscle weakness, steroid myopathy, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fractures, tendon rupture - particularly of the Achilles tendon.

**Gastrointestinal** - Peptic ulcer with possible subsequent perforation and hemorrhage, pancreatitis, gastrointestinal hemorrhage, esophagitis, perforation of the bowel.

Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT) and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.

**Dermatologic** - Impaired wound healing, thin fragile skin, petechiae and ecchymosis.

**Neurological** - Increased intracranial pressure, pseudotumor cerebri, psychic derangements, seizures.

**Endocrine** - Menstrual irregularities, development of Cushingoid state, suppression of growth in children, suppression of pituitary - adrenal axis, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics.

**Ophthalmic** - Posterior subcapsular cataracts, increased intraocular pressure, exophthalmos.

**Metabolic** - Negative nitrogen balance due to protein catabolism.

**Immune System** - Masking of infections, latent infections becoming active, opportunistic infections, hypersensitivity reactions including anaphylaxis, may suppress reactions to skin tests.

**B. Lidocaine**

Central Nervous System

Lightheadedness	Vomiting
Nervousness	Sensation of heat, cold, numbness
Apprehension	Twitching
Euphoria	Tremors
Confusion	Convulsions
Dizziness	Loss of consciousness
Drowsiness	Respiratory depression
Tinnitus	Respiratory arrest
Blurred or double vision	

Cardiovascular System

Bradycardia	Cardiovascular collapse
Hypotension	Cardiac arrest

### Allergic Reactions

Cutaneous lesions

Edema

Urticaria

Anaphylactic reactions

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There is no clinical syndrome of acute overdosage with DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride). Repeated frequent doses (daily or several times per week) over a protracted period may result in a Cushingoid state, and other complications of chronic steroid therapy.

### **DOSAGE AND ADMINISTRATION**

Because of possible physical incompatibilities, DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride) should not be diluted or mixed with other solutions. Parenteral suspensions should be inspected visually for foreign particulate matter and discoloration prior to administration whenever drug product and container permit.

### **ADMINISTRATION FOR LOCAL EFFECT**

Therapy with DEPO-MEDROL with Lidocaine does not obviate the need for the conventional measures usually employed. Although this method of treatment will ameliorate symptoms, it is in no sense a cure and the hormone has no effect on the cause of the inflammation.

1. **Rheumatoid and Osteoarthritis**

The dose for intra-articular administration depends upon the size of the joint and varies with the severity of the condition in the individual patient. In chronic cases, injections may be repeated at intervals ranging from one to five or more weeks depending upon the degree of relief obtained from the initial injection. The doses in the following table are given as a general guide:

<b>Size of Joint</b>	<b>Examples</b>	<b>Range of Dosage (methylprednisolone acetate)</b>
Large	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	10 to 40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

Procedure: It is recommended that the anatomy of the joint involved be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect, it is important that the injection be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile 20 to 24 gauge needle (on a dry syringe) is quickly inserted into the synovial cavity. Procaine infiltration is elective. The aspiration of only a few drops of joint fluid proves the joint space has been entered by the needle.

The injection site for each joint is determined by that location where the synovial cavity is most superficial and most free of large vessels and nerves. With the needle in place, the aspirating

syringe is removed and replaced by a second syringe containing the desired amount of DEPO-MEDROL with Lidocaine. The plunger is then pulled outward slightly to aspirate synovial fluid and to make sure the needle is still in the synovial space. After injection, the joint is moved gently a few times to aid mixing of synovial fluid and the suspension. The site is covered with a small sterile dressing.

Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal, and hip joints. Since difficulty is occasionally encountered in entering the hip joint, precautions should be taken to avoid any large blood vessels in the area. Joints not suitable for injection are those that are anatomically inaccessible such as the spinal joints and those like the sacroiliac joints that are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the joint space. Little or no benefit follows injection into surrounding tissue. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile. Local therapy does not alter the underlying disease process, and whenever possible comprehensive therapy including physiotherapy and orthopedic correction should be employed.

Following intra-articular steroid therapy, care should be taken to avoid overuse of joints in which symptomatic benefit has been obtained. Negligence in this matter may permit an increase in joint deterioration that will more than offset the beneficial effects of the steroid.

Unstable joints should not be injected. Repeated intra-articular injection may in some cases result in instability of the joint. X-ray follow-up is suggested in selected cases to detect deterioration.

If a local anesthetic is used prior to injection of DEPO-MEDROL with Lidocaine, the anesthetic package insert should be read carefully and all the precautions observed.

2. **Bursitis**

The area around the injection site is prepared in a sterile way and a wheal at the site made with 1 percent procaine hydrochloride solution. A 20 to 24 gauge needle attached to a dry syringe is inserted into the bursa and the fluid aspirated. The needle is left in place and the aspirating syringe changed for a small syringe containing the desired dose. After injection, the needle is withdrawn and a small dressing applied.

3. **Miscellaneous: Ganglion, Tendinitis, Epicondylitis**

In the treatment of conditions such as tendinitis or tenosynovitis, care should be taken, following application of a suitable antiseptic to the overlying skin, to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when placed on a stretch. When treating conditions such as epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into the area. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst.

The usual sterile precautions should be observed, of course, with each injection.

The dose in the treatment of the various conditions of the tendinous or bursal structures listed above varies with the condition being treated and ranges from 4 to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary.

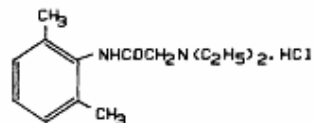
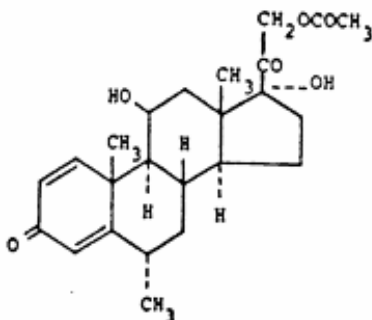
When multidose vials are used, special care to prevent contamination of the contents is essential (See WARNINGS).

## PHARMACEUTICAL INFORMATION

### Drug Substance

	<b>DEPO-MEDROL</b>	<b>Lidocaine</b>
<b>Proper Name</b>	sterile methylprednisolone acetate USP	lidocaine hydrochloride USP
<b>Chemical Name:</b>	(1) Pregna-1,4-diene-3,20-dione,21-(acetyloxy)-11,17-di-hydroxy-6-methyl, (6 $\alpha$ , 11 $\beta$ -;(2)11 $\beta$ ,17,21-trihydroxy-6 $\alpha$ -methylpregna-1,4-diene-3,20-dione 21-acetate	(1) Acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate;(2)2-(Diethylamino)-2',6'-acetoxylidide monohydrochloride monohydrate

**Structural formula:**



**Molecular Formula:** C<sub>24</sub>H<sub>32</sub>O<sub>6</sub>

C<sub>14</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O

**Molecular Weight:** 416.51

234.34

**Description:**

Methylprednisolone acetate is the 6-methyl derivative of prednisolone. It is a white or practically white, odorless, crystalline powder which melts at about 215°C with some decomposition. It is soluble in dioxane, sparingly soluble in acetone, in alcohol, in chloroform, and in methanol, and slightly soluble in ether. It is practically insoluble in water.

Lidocaine hydrochloride is very soluble in water, alcohol; soluble in chloroform and insoluble in ether. The melting point is between 74°C to 79°C. Lidocaine has a pKa of 7.68 and a partition coefficient of 1.65 at pH 7.4.

**Composition:**

Each mL of this preparation contains:

methylprednisolone acetate USP	40.0 mg
lidocaine HCl USP	10.0 mg
polyethylene glycol 3350 NF	29.1 mg
benzyl alcohol NF	9.2 mg
sodium chloride	6.6 mg
myristyl-gamma-picolinium chloride	0.2 mg
water for injection	qs

When necessary, pH was adjusted with Sodium Hydroxide and/or Hydrochloric Acid. The pH of the finished product remains within the U.S.P. specified range i.e. 3.5 to 7.0.

**Stability and storage recommendations:**

Store at room temperature (15°C to 30°C). Protect from freezing.

**AVAILABILITY OF DOSAGE FORMS**

DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride) is available in 1, 2 and 5 mL vials containing 40 mg/mL methylprednisolone acetate and 10 mg/mL lidocaine hydrochloride.

## TOXICOLOGY

### Animal

The LD<sub>50</sub> of lidocaine alone given intraperitoneally to albino mice was found to be 126 ± 4.6 mg/kg. Pretreatment of similar mice with as high as 0.5 mg/kg of methylprednisolone did not significantly alter the acute toxicity of lidocaine.

Acute intra-articular irritation studies were performed in albino rabbits using 0.25 mL of each of methylprednisolone acetate and lidocaine hydrochloride, methylprednisolone acetate alone or saline. Four days after the injection of one of these materials, no significant abnormalities of synovial fluid, synovial membranes or articulating surfaces of these joints could be found.

A six week parenteral toxicity study in rats to characterize the systemic subacute toxicity of a combination of methylprednisolone acetate and lidocaine was performed. No findings other than those attributable to the glucocorticoid content of the product were found, nor were there any histological changes found in these animals which could not be attributed to treatment with either methylprednisolone or lidocaine alone.

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