הודעה על החמרה (מידע בטיחות)

תאריך: 28/10/2012

שם תכשיר באנגלית: DEPO MEDROL WITH LIDOCAINE

מספר רישום: 045.97.23829.00

שם בעל הרישום: פייזר פרמצבטיקה ישראל בע"מ

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
4.2 Posology and Method of Administration Because of possible physical incompatibilities, methylprednisolone acetate with lidocaine should not be diluted or mixed with other solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Therapy with methylprednisolone acetate 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. …	**Indications** Therapy with methylprednisolone acetate 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. …	**4. CLINICAL PARTICULARS**
4.3 Contraindications Methylprednisolone acetate with Lidocaine is contraindicated : • in patients who have systemic fungal infections • in patients with known hypersensitivity to methylprednisolone or any component of the formulation • in patients with known hypersensitivity to Lidocaine or other local anesthetics of the amide type • for use by the intrathecal route of administration • for use by the intravenous route of administration Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.	**Contra-indications** - systemic fungal infections - known hypersensitivity to components and to local anesthetics of the amide type	
4.4 Special Warnings and Precautions for Use **Immunosuppressant Effects/increased Susceptibility to Infections** Corticosteroids may increase susceptibility to infection, 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.	**INTRA-ARTICULAR USE** Following intra-articular corticosteroid 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	**Warnings and Precautions**

Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic ~~infections~~ organisms, 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-synovial, intrabursal or intratendinous administration for local effect in the presence of acute infection.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

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.

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.

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

Immune System Effects

Allergic reactions may occur. Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions have occurred in patients receiving corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

Endocrine Effects

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

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy.

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.
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 intrasynovial injection should include precautions against injection or leakage into the dermis.
Appropriate measures must be taken to avoid intravascular injections.
In patients on corticosteroid therapy subjected to 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 infectiori when corticosteroids are used Do not use intrasynovially, intrabursally or intratendinous administration for local effect in the presence of acute infection.
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 anaphylactic reactions have occurred in patients receiving parenteralcorticosteroid therapy, appropriate precautionary measures should be taken prior to administration,especially when the patient has a history of allergy to any drug.~~
~~Allergic skin reactions have been reported apparently related to the excipients. Rarely has skin testing demonstrated a reaction to methylprednisolone acetate, per se.~~
Corticosteroids should be used with caution in non specific 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.
No evidence exists showing that corticosteroids are carcinogenic, mutagenic or impair fertility.
This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.
Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" in premature infants.

THE FOLLOWING ADDITIONAL PRECAUTIONS APPLY FOR PARENTERAL CORTICOSTEROIDS
- intrasynovial injection of a corticosteroid may produce systemic as well as local effects;
- appropriate examination of any joint fluid present is necessary to exclude a septic

Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease. [3]

There is an enhanced effect of corticosteroids on patients with hypothyroidism.

Metabolism and Nutrition

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric Effects

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.

Potentially severe psychiatric adverse reactions may occur with systemic steroids. Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Nervous System Effects

Corticosteroids should be used with caution in patients with seizure disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis (Also see myopathy statement in Musculoskeletal Effects section below).

Ocular Effects

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma, with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.
Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation.

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.

RELATIVE CONTRA-INDICATIONS

Special risk groups

Children, diabetics, hypertensive patients and patients with psychiatric antecedents, certain infectious diseases such as tuberculosis or certain viral diseases such as herpes and zona associated with ocular symptoms should be under strict medical surveillance and should be treated during an as short as possible period (see also sections SPECIAL PRECAUTIONS and ADVERSE REACTIONS).

THE FOLLOWING ADDITIONAL PRECAUTIONS APPLY FOR PARENTERAL CORTICOSTEROIDS

- intrasynovial injection of a corticosteroid may produce systemic as well as local effects;
- appropriate examination of any joint fluid present is necessary to exclude a septic process;
- a marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted;
- local injection of a steroid into a previously infected joint is to be avoided;
- corticosteroids should not be injected into unstable joints. Sterile technique is necessary to prevent infections or contamination.

Cardiac Effects

Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed.

Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Vascular Effects

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal Effects

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or hemorrhage may occur without significant pain.
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.

Hepatobiliary Effects

High doses of corticosteroids may produce acute pancreatitis.

Musculoskeletal Effects

An acute myopathy has been reported 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 anticholinergics, such as neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Renal and Urinary Disorders

Corticosteroids should be used with caution in patients with renal insufficiency.

Investigations Average and large doses of hydrocortisone or cortisone 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. **Other Warnings and Precautions** Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increased risk for osteoporosis, as well as increased risk for fluid retention with possible resultant hypertension. Since complications of treatment with glucocorticoids are dependent on the amount 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 as to whether daily or intermittent therapy should be used. Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids. **Use in Children** This product contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily-divided dose glucocorticoid therapy and use of such a regimen should be restricted to those most serious indications. Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure. High doses of corticosteroids may produce pancreatitis in children.		
4.5 Interaction with Other Medicaments and Other Forms of Interaction Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme (see **Table 2**). CYP 3A4 INHIBITORS – Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration	**UNDESIRED INTERACTIONS** ~~- Corticosteroids may increase renal clearance of salicylates.~~ ~~- This could lead to a decrease in salicylate serum levels or increase the risk of salicylate toxicity~~ ~~- when corticoids are withdrawn. .~~ ~~- Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticoids.~~ ~~- Therefore the dose of corticoid should be titrated to avoid overdosage.~~ ~~- Concurrent administration of barbiturates, phenylbutazone, phenytoin or rifampicin may enhance the metabolism and reduce the effects of corticoids.~~ ~~- There are reports. of enhanced as well as~~	**INTERACTIONS**

of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity (see **Table 2**). CYP 3A4 INDUCERS – Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result (see **Table 2**). CYP 3A4 SUBSTRATES – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be inhibited or induced, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration (see **Table 2**). NON-CYP 3A4 - MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are described below (see **Table 2**). **Table 2: Important drug or substance interactions/effects with methylprednisolone** **…**	~~diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore coagulation indices should be monitored to maintain the desired anticoagulant effect.~~ ~~- While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids,~~ ~~especially on high doses because of possible hazards of neurological complications and lack of antibody response.~~ ~~- Glucocorticoids may increase the requirements for insulin or oral hypoglycemic agents in diabetics.~~ ~~Combination of glucocorticoids with thiazid-diuretics increases the risk of glucose intolerance.~~ ~~- Concurrent use of ulcerogenic drugs (e.g. salicylates. NSAI drugs) may increase the risk of gastrointestinal ulceration.~~ ~~- Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.~~ ~~- Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin.~~ ~~Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and Methylprednisolone, therefore it is possible that convulsions and other adverse events associated with the individual use of either drug may be more apt to occur.~~ ~~- No additional benefit derives from the IM administration of DEPO-MEDROL™ with Lidocaine.~~ ~~Where parenteral corticosteroid therapy for sustained systemic effect is desired, plain DEPO-MEDROL™ should be used.~~	
4.6 Fertility, pregnancy and lactation <u>Fertility</u> No evidence exists showing that corticosteroids are carcinogenic, mutagenic or impair fertility. <u>Pregnancy</u> 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 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. Corticosteroids and Lidocaine readily cross the placenta. One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids.	**Pregnancy and lactation** Some animal studies have shown that corticosteroids, when administered to the mother at high doses, may cause fetal malformations. Adequate human reproduction studies have not been done with corticosteroids or lidocaine. Therefore the use of this drug in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Corticosteroids should be used in pregnancy only if clearly needed. Corticosteroids and lidocaine diffuse across the placenta. New born infants born of mothers who have received substantial doses of glucocorticosteroids during pregnancy, should be carefully observed and evaluated for signs of adrenal insufficiency. Corticosteroids are excreted in breast milk. It is not known whether lidocaine is excreted in human breast milk. The use of local anesthetics such as lidocaine during labor and delivery may be associated with adverse effects on mother and fetus. There are no known effects of	**Fertility, pregnancy and lactation**

Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. Although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids, those exposed to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency. The use of local anesthetics such as Lidocaine during labor and delivery may be associated with adverse effects on mother and fetus. There are no known effects of corticosteroids on labor and delivery Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy. Lactation Corticosteroids are excreted in breast milk. It is not known whether Lidocaine is excreted in human breast milk. Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infant. **4.7 Effects on Ability to Drive and Use Machines** The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.	corticosteroids on labor and delivery. INTRA-ARTICULAR USE … No evidence exists showing that corticosteroids are carcinogenic, mutagenic or impair fertility. …	**Effects on Ability to Drive and Use Machines**
4.8 Undesirable Effects **A. Adverse Drug Reactions Occurring with Methylprednisolone acetate… (table)** **B. Adverse Drug Reactions Occurring with Lidocaine… (table)**	**Adverse reactions** A. ADVERSE REACTIONS RELATED TO METHYLPREDNISOLONE ACETATE Systemic adverse reactions may be observed. Although rarely occurring in very short term therapy, they should always be carefully traced. This is part of the follow-up of any corticotherapy, and does not specifically pertain to any particular product. - Fluid and electrolyte disturbances In comparison with cortisone or hydrocortisone, mineralocorticoid effects are less likely to occur with synthetic derivatives as methylprednisolone acetate.	**Adverse reactions**

	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 Pathologic fracture -Gastrointestinal Peptic ulceration with possible perforation and hemorrhage Gastric hemorrhage Pancreatitis Esophagitis Perforation of the bowel Increases in SGPT, SGOT and alkaline phosphatase have been observed. 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 Seizures Psychic derangements may appear when glucocorticoids are used ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations. - Endocrine Menstrual irregularities Development of Cushingoid state Suppression of pituitary-adrenal axis Decreased carbohydrate tolerance Manifestations of latent diabetes mellitus Increased requirements for insulin or oral hypoglycemic agents in diabetics Suppression of growth in children - Ophthalmic Prolonged use of glucocorticoids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses. Glucocorticoids should be used cautiously in patients with ocular herpes simplex for fear of corneal perforation. 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 - In situ administration In situ administration can cause dermal and subdermal atrophy, While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physiochemical 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 (see SPECIAL PRECAUTIONS). Regeneration is usually complete within a few months or after all crystals of the adrenal steroid have been absorbed. - The following additional reactions are related to parenteral corticosteroid therapy Rare instances of blindness associated with intralesional therapy around the face and head Anaphylactic or allergic reactions Hyperpigmentation or hypopigmentation Subcutaneous and cutaneous atrophy Sterile abscess Postinjection flare, following intrasynovial use Charcot-like arthropathy Injection site infections following non sterile technique B. ADVERSE REACTIONS RELATED TO LIDOCAINE HYDROCHLORIDE - Central nervous system Lightheadedness or dizziness Nervousness Apprehension Euphoria Confusion Drowsiness Tinnitus Blurred or double vision Vomiting Sensation of heat. cold. numbness Twitching Tremors Convulsions Loss of consciousness Respiratory depression Respiratory arrest - Cardiovascular system Bradycardia Hypotension Cardiovascular collapse Cardiac arrest - Allergic reactions Cutaneous lesions Urticaria Edema Anaphylactic reactions C. ADVERSE REACTIONS REPORTED WITH SOME NON RECOMMENDED ROUTES OF ADMINISTRATION - Intrathecal/Epidural	

	Arachnoiditis, meningitis. paraparesis/paraplegia, sensory disturbances, bowel/bladder dysfunction. headache. seizures - Intranasal Temporary/permanent visual impairment including blindness, allergic reactions, rhinitis - Ophthalmic Temporary/permanent visual impairment including blindness, increased intraocular pressure, ocular and periocular inflammation including allergic reactions, infection, residue or slough at injection site - Miscellaneous injection sites (scalp. tonsillar fauces, sphenopalantine ganglion) Blindness	
4.9 Overdosage Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. Methylprednisolone is dialyzable.	**Overdosage** ~~There is no clinical syndrome of acute overdosage with methylprednisolone acetate. 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. Overdosage of lidocaine hydrochloride may produce convulsions, bradycardia, hypotension and respiratory arrest.~~	**Overdosage**
5. PHARMACOLOGICAL PROPERTIES **5.1 Pharmacodynamic Properties** Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention. Lidocaine hydrochloride is a local anesthetic which reversibly blocks nerve conduction near the site of application or injection. **5.2 Pharmacokinetic Properties** One in-house study of eight volunteers determined the pharmacokinetics of a single 40 mg intramuscular dose of Methylprednisolone acetate. The average of the individual peak plasma concentrations was 14.8 ± 8.6 ng/mL, the average of the individual peak times was 7.25 ± 1.04 hours, and the average area under the curve (AUC) was 1354.2 ± 424.1 ng/mL x hrs (Day 1-21). Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. The plasma protein binding of methylprednisolone in humans is approximately 77%. In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4. (For a list of	**PHARMACODYNAMICS** Methylprednisolone acetate has the general properties of methylprednisolone but is less soluble and less readily metabolised, which explains its prolonged activity. It has a greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention, potassium loss and hypertension. Like methylprednisolone, methylprednisolone acetate advantages over the older corticoids lies in its ability to achieve equal anti-inflammatory effects with lower dose. A dose of 4.4 mg methylprednisolone acetate is considered to be equivalent to 20 mg hydrocortisone Glucocorticoids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin) and stimulate transcription of mRNA and subsequent protein synthesis of various enzymes thought to be ultimately responsible for the effects of systemic use of adrenocorticoids. Maximum pharmacologic activity of corticosteroids lays behind peak blood levels, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct actions by the drug. Lidocaine hydrochloride produces insensitivity and loss of pain without loss of nervous control by preventing or diminishing the conduction of sensory nerve impulses along nerve fibres and at nerve endings. When injected lidocaine hydrochloride has a rapid onset of action and its effects are	**PHARMACOLOGICAL PROPERTIES**

drug interactions based on CYP3A4-mediated metabolism, see section 4.5 **Interactions with Other Medicinal Products and Other Forms of Interaction**).

The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours.
Its apparent volume of distribution is approximately 1.4 L/kg, and its total clearance is approximately 5 to 6 mL/min/kg.

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

No dosing adjustments are necessary in renal failure. Methylprednisolone is hemodialyzable.

There are no human pharmacokinetic data for lidocaine or Depo-Medrol with lidocaine injected intra-articularly or into the joint.

5.3 Preclinical Safety Data

Methylprednisolone

Based on conventional studies of safety pharmacology, repeated- dose toxicity in mice, rats, rabbits, and dogs using intravenous, intraperitoneal, subcutaneous, intramuscular, and oral routes of administration, no unexpected hazards were identified. The toxicities seen in the repeated-dose studies are those expected to occur with continued exposure to exogenous adrenocortical steroids.

Carcinogenic potential:
Long-term studies in animals have not been performed to evaluate carcinogenic potential, as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity. There is no evidence that corticosteroids are carcinogenic.

Mutagenic potential:
There was no evidence of a potential for genetic and chromosome mutations when tested in a DNA damage/alkaline elution assay in Chinese hamster V 79 cells. Methylprednisolone did not induce chromosomal damage in the absence of a liver activation system.

Reproductive toxicity:
An increased frequency of cleft palate was observed among the offspring of mice treated during pregnancy with methylprednisolone in doses similar to those typically used for oral therapy in humans. A typical dose-response relationship was seen.

An increased frequency of cardiovascular defects and decreased body weight were observed among the offspring of pregnant rats treated with methylprednisolone in a dose that was similar to

more
intense and prolonged than those of procaine and are reversible.

PHARMACOKINETICS
Methylprednisolone acetate is hydrolysed to its active form by serum cholinesterases.
In man, methylprednisolone forms a weak dissociable bond with albumin and transcortin. Approximately 40 to 90% of the drug is bound.
Metabolism of methylprednisolone occurs via hepatic routes qualitatively similar to that of cortisol. The major metabolites are 20-beta-hydroxymethylprednisolone and 20-beta-hydroxy-6-alpha-methy1prednisone. The metabolites are excreted in the urine as glucuronides, sulfates and unconjugated compounds. These conjugation reactions occur principally in the liver and to some extent in the kidney.
The plasma half-lives of steroids are generally short as compared to the biological half-lives; long after measurable plasma levels of steroids are depleted pharmacological activities continue.
An intra-articular injection of 40 mg in both knees (total dose 80 mg) gives after 4 to 8 hours methylprednisolone peaks of approximately 21.5 μg/100 ml.
After intra-articular administration methylprednisolone acetate diffuses from the joint into systemic
circulation over approximately 7 days.
Lidocaine hydrochloride is rapidly absorbed from injection sites and rapidly spreads through surrounding tissues. It penetrates into the cerebrospinal fluid and diffuses across the placenta. Lidocaine is rapidly de-ethylated to monoethylglycine exylidide than metabolised by amidases in the liver. Less than 10% is excreted unchanged. The metabolic products are excreted in the urine.

that used for oral therapy in humans but was toxic to the mothers. In contrast, no teratogenic effect was noted in rats with doses <1-18 times those typically used for oral therapy in humans in another study. High frequencies of fetal death and a variety of central nervous system and skeletal anomalies were reported in the offspring of pregnant rabbits treated with methylprednisolone in doses less than those used in humans. The relevance of these findings to the risk of malformations in human infants born to mothers treated with methylprednisolone early in pregnancy is unknown. **Lidocaine** Carcinogenic potential: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Oral and subcutaneous LD_{50} values in mice ranged between ~ 160 and ~ 400 mg/kg body weight (bw) while intramuscular LD50 values of lidocaine in rats were 260 mg/kg bw. No studies concerning repeated dose toxicity were provided. Mutagenic potential: Genotoxicity studies were carried out with lidocaine and its metabolites. The *Salmonella* microsomal assay *(Salmonella typhimurium* strains TA100, TA98, and TA1538 with 1, 10, 100 and 500 mg/plate), with or without metabolic activation, with lidocaine and its metabolites mono-ethylglycinexylidine, N-hydroxylidocaine, N-hydroxy-monoethylglycinexylidine, 2,6-xylidine, 2,6-dimethylphenylhydroxylamine, did not reveal any mutagenic activity. However these studies were poorly carried out. Reproductive toxicity: A study was conducted on male and female rats administered orally 30 mg/kg bw of lidocaine daily for 8 months. During that period, 3 matings were conducted and reproductive parameters were analysed for each gestation, as well as offspring development up to weaning. No effects could be detected. **Methylprednisolone plus Lidocaine** Carcinogenic potential: Long-term studies in animals have not been performed to evaluate carcinogenic potential. The LD50 of lidocaine alone given intraperitoneally to albino mice was found to be 126 ± 4.6 mg/kg. Pretreatment of these 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 performed in albino rabbits using 0.25 mL of each of methylprednisolone acetate and lidocaine hydrochloride, methylprednisolone acetate alone or saline for four days after the injection of one of		

these materials showed no significant abnormalities of synovial fluid, synovial membranes or articulating surfaces of these joints. A six week parenteral toxicity study in rats to characterize the systemic subacute toxicity of a combination of methylprednisolone acetate and lidocaine showed no findings other than those attributable to the glucocorticoid content of the product, nor were there any histological changes found in these animals which could not be attributed to treatment with either methylprednisolone or lidocaine alone. Mutagenic potential: Genotoxicity studies have not been conducted with the combination of methylprednisolone and lidocaine (see above for genotoxicity as it pertains to the individual drugs). Reproductive toxicity: Reproductive toxicity studies have not been conducted with the combination of methylprednisolone and lidocaine (see above for reproductive toxicity as it pertains to the individual drugs).		