PRODUCT MONOGRAPH

[Pr]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.
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Kirkland, Quebec, H9J 2M5

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PRODUCT MONOGRAPH

PrDEPO-MEDROL* WITH LIDOCAINE

(sterile methylprednisolone acetate suspension USP with lidocaine hydrochloride)

Glucocorticoid with local anaesthetic

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intra-synovial Injection (including periarticular and intrabursal)	40 mg/mL methylprednisolone acetate + 10 mg/mL lidocaine hydrochloride sterile aqueous suspension	Benzyl alcohol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

FOR INTRA-SYNOVIAL OR SOFT TISSUE ADMINISTRATION

(including periarticular and intrabursal) SEE WARNINGS AND PRECAUTIONS

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

DEPO-MEDROL with Lidocaine is contraindicated:

- in patients with known hypersensitivity to any components of DEPO-MEDROL, Lidocaine or other local anesthetics of the amide type.
- in patients with systemic fungal infections.

- in idiopathic thrombocytopenic purpura when administered intramuscularly
- in patients administered with live or live, attenuated vaccines while receiving immunosuppressive doses of corticosteroids.
- in herpes simplex of the eye, except when used for short-term or emergency therapy as in acute sensitivity reactions.
- in patients with vaccinia and varicella, except when used for short-term or emergency therapy as in acute sensitivity reactions.

DEPO-MEDROL with Lidocaine is not indicated for epidural, intravenous and intrathecal administration. Reports of serious medical events, including death, have been associated with epidural and intrathecal routes of corticosteroid administration .

DEPO-MEDROL with Lidocaine is contraindicated for use in premature infants because the formulation contains benzyl alcohol. See WARNINGS AND PRECAUTIONS, Special Populations; Pediatrics.

WARNINGS AND PRECAUTIONS

General

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. 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.

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

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 AND CLINICAL USE. It is critical that, during administration of DEPO-MEDROL with Lidocaine appropriate technique be used and care taken to assure proper route of administration.

Serious medical events have been reported with the intrathecal/epidural routes of administration (See CONTRAINDICATIONS and ADVERSE REACTIONS). 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.

DEPO-MEDROL with Lidocaine should not be used in premature infants. The formulation contains benzyl alcohol, which has been reported to be associated with a fatal "gasping syndrome" in premature infants. 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 at which toxicity may occur is not known. See also CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Pediatrics.

Caution must be used in 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 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.

Intra-articular injected corticosteroids may be systemically absorbed.

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

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis. A metabolite of lidocaine, 2,6-xylidine, has shown weak genotoxic potential in vitro and in vivo and carcinogenic potential (in rats) with unknown clinical relevance in relation to short-term/intermittent use of lidocaine as a local anaesthetic (see Toxicology).

Cardiovascular
Literature reports suggest an apparent association between the 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.

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution, and only if strictly necessary, in patients with congestive heart failure. Corticosteroids should also be used with caution in hypertension, or renal insufficiency (see also WARNINGS AND PRECAUTIONS, Endocrine and Metabolism; ADVERSE REACTIONS).

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.

Endocrine and Metabolism
Patients should be monitored for Hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome and hyperglycemia with chronic use.

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. 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. In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

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

Average and large doses of cortisone or hydrocortisone 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. See also WARNINGS AND PRECAUTIONS, Cardiovascular.

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

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

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids, including methylprednisolone. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

Gastrointestinal
Corticosteroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, in diverticulitis, fresh intestinal anastomoses and active or latent peptic ulcer, when steroids are used as direct or adjunctive therapy, 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.

Glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

Hematologic
Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. See also DRUG INTERACTIONS.

Hepatic/Biliary/Pancreatic
There is an enhanced effect of corticosteroids in patients with cirrhosis.

High doses of corticosteroids may produce acute pancreatitis.

Immune
Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. 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 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-synovially, intrabursally, or for intratendinous administration for local effect in the presence of acute infection.

Recent studies suggest that corticosteroids should not be used in septic shock (an unapproved indication), and suggest that increased mortality may occur in some subgroups at higher risk (e.g. elevated serum creatinine greater than 2.0 mg/dL or secondary infections).

Fungal Infections
Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see CONTRAINDICATIONS; DRUG INTERACTIONS).

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, Taxoplasma.

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 Stronglyoides 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. There is currently no evidence of benefit from steroids in this condition.

Tuberculosis
The use of DEPO-MEDROL with Lidocaine in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

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.

Vaccinations
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see CONTRAINDICATIONS). Killed or inactivated vaccines may be administered; however the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

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 in high doses, because of possible hazards of neurological complications and lack of antibody response.

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.

Musculoskeletal
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, see WARNINGS AND PRECAUTIONS - Neurologic), 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.

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in 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 increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy.

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

Neurologic
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 systemic corticosteroids, including DEPO-MEDROL with Lidocaine, should not be used for the treatment of traumatic brain injury.

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

Corticosteroids should be used with caution in patients with myasthenia gravis.

There have been reports of epidural lipomatosis in patients taking corticosteroids (including reports in children).

Ophthalmologic
Use of corticosteroids may produce posterior sub-capsular 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. As intraocular pressure may become elevated in some individuals, if steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

The use of systemic corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

Psychiatric
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.

Sensitivity/Resistance
Allergic reaction 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 patients have a history of allergy to any drug.

Sexual Function/Reproduction
Steroids may increase or decrease motility and number of spermatozoa in some patients.

Special Populations

Fertility:
Corticosteroids have been shown to impair fertility in animal studies.

Pregnant Women:

Methylprednisolone
Corticosteroids readily cross the placenta. Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits, have yielded an increase incidence of cleft palate in the off-spring. There are no adequate and well-controlled studies in pregnant women.

Since there is inadequate evidence of safety in human pregnancy, this drug should be used in pregnancy or by women of child bearing potential only if clearly needed and the potential benefit justifies the potential risk to the mother and embryo or fetus. Infants born to mothers who have

received corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. There are no known effects of corticosteroids on labour and delivery.

One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Lidocaine
The use of local anesthetics such as lidocaine during labor and delivery may be associated with adverse effects on mother and fetus.

Adequate human reproductive studies have not been done with Lidocaine.

Lidocaine readily crosses the placenta.

Benzyl alcohol
Benzyl alcohol can cross the placenta.

Nursing Women:

Methylprednisolone
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.

Lidocaine
It is not known whether lidocaine is excreted in breast milk.

Pediatrics: Benzyl alcohol, a component of this product, has been associated with serious adverse events including death, particularly in pediatric patients, including the "gasping syndrome" in neonate and low-birth weight infants. The "gasping syndrome" is 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. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. 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.

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. Pediatric patients may experience a decrease in their growth velocity at low systemic doses and in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression (e.g., 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. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be titrated to the lowest effective dose.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. 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.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Geriatrics
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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.

Monitoring and laboratory testing
Corticosteroids may suppress reactions to skin tests.

Dosage adjustments may be required based on the following conditions: during remission or exacerbation of the disease process; the patient's individual response to therapy; or upon exposure of the patient to emotional or physical stress such as serious infection, surgery or injury.

Monitoring for signs and symptoms of drug-induced secondary adrenocortical insufficiency may be necessary for up to one year following cessation of long-term or high-dose corticosteroid therapy.

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 disturbance and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

ADVERSE REACTIONS

The following adverse reactions have been reported with Lidocaine and DEPO-MEDROL or other corticosteroids:

A. DEPO-MEDROL (methylprednisolone acetate)

MedDRA (v15) System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Common	Infection
	Not known	Opportunistic infection; peritonitis; injection site infections (following non-sterile technique); decreased resistance to infection;
Blood and lymphatic system disorders	Not known	Leukocytosis
Immune system disorders	Not known	Drug hypersensitivity; anaphylactic reaction
Endocrine disorders	Common	Cushingoid
	Not known	Hypopituitarism (particularly in times of stress, as in trauma, surgery, or illness); moon face; weight gain; abnormal fat deposits; glycosuria; hypertrichosis; steroid withdrawal syndrome
Metabolism and nutrition disorders	Common	Sodium retention; fluid retention; glucose tolerance impaired; increased requirements for insulin (or oral hypoglycemic agents in diabetics)
	Not known	Alkalosis hypokalaemic, dyslipidemia; increased appetite (which may result in weight increased); lipomatosis
Psychiatric disorders	Common	Affective disorder (including depressed mood, euphoric mood); mood swings; abnormal behaviour; insomnia
	Not known	Affective disorder (including affect lability, psychological dependence, suicidal ideation); psychotic disorder (including mania, delusion, hallucination, schizophrenia [aggravation of]); confusional state; mental disorder; anxiety; personality

MedDRA (v15) System Organ Class	Frequency	Undesirable Effect
		change; emotional instability
Nervous system disorders	Not known	Intracranial pressure increased (with papilloedema [idiopathic intracranial hypertension] usually following discontinuation of treatment); convulsion; amnesia; cognitive disorder, dizziness headache; neuritis; neuropathy; paresthesia, epidural lipomatosis
Eye disorders	Common	Cataract; glaucoma
	Not known	Exophthalmos; increased intraocular pressure; central serous chorioretinopathy
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Cardiac failure (in susceptible patients); bradycardia; tachycardia; cardiac arrest; cardiac arrhythmias; cardiac enlargement; circulatory collapse; fat embolism; hypertrophic cardiomyopathy in premature infants; myocardial rupture following recent myocardial infarction; pulmonary oedma; syncope; thromboembolism; thrombophlebitis; vasculitis
Vascular disorders	Common	Hypertension
	Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Hiccups
Gastrointestinal disorders	Common	Peptic ulcer (with possible subsequent peptic ulcer perforation and peptic ulcer haemorrhage)
	Not known	Gastric haemorrhage; intestinal perforation (particularly in patients with inflammatory bowel disease); pancreatitis; oesophagitis ulcerative ; oesophagitis; abdominal pain; Abdominal distension; diarrhoea; dyspepsia; nausea; bowel/bladder dysfunction

MedDRA (v15) System Organ Class	Frequency	Undesirable Effect
		(after intrathecal administration), elevation in serum liver enzyme levels (usually reversible upon discontinuation), increased appetite;
Hepatic disorders	Not known	Hepatomegaly
Skin and subcutaneous disorders	Common	Ecchymoses; acne
	Not known	Angioedema; petechiae; skin atrophy; skin striae; skin hyperpigmentation; skin hypopigmentation; hirsutism; rash; erythema; pruritus; urticaria; hyperhidrosis; allergic dermatitis; cutaneous and subcutaneous atrophy; dry scaly skin; sterile abscess; thinning scalp hair; post-injection flare – following intra-synovial use; Kaposi's sarcoma
Musculoskeletal and connective tissue disorders	Common	Growth retardation; osteoporosis; muscular weakness
	Not known	Osteonecrosis; pathological fracture; muscle atrophy; myopathy; arthralgia; myalgia; calcinosis (following intra-articular or intralesional use); Charcot-like arthropathy; postinjection flare (following intra-articular use); spinal compression fracture
Reproductive system and breast disorders	Not known	Menstruation irregular; increased or decreased motility and number of spermatozoa
General disorders and administration site conditions	Common	Impaired healing; oedema peripheral; irritability; injection site reaction
	Not known	Fatigue; malaise
Investigations	Common	Blood potassium decreased
	Not known	Alanine aminotransferase increased; aspartate aminotransferase increased; blood alkaline phosphatase increased; carbohydrate tolerance decreased; urine

MedDRA (v15) System Organ Class	Frequency	Undesirable Effect
		calcium increased; suppression of reactions to skin tests; Nitrogen balance negative (due to protein catabolism); blood urea increased
Injury, poisoning and procedural complications	Not known	Tendon rupture (particularly of the Achilles tendon)

B. <u>Lidocaine</u>

MedDRA (v15) System Organ Class	Frequency	Undesirable Effect
Immune system	Not known	Anaphylactic reaction
Psychiatric disorders	Common	Confusional state; euphoric mood; nervousness; anxiety
Nervous system disorders	Common	Loss of consciousness; convulsion; hypoaesthesia; tremor; somnolence; dizziness; light-headedness; numbness
Eye disorders	Common	Diplopia; vision blurred
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Common	Bradycardia
Vascular disorders	Common	Hypotension
	Not known	Cardiac arrest; circulatory collapse
Respiratory, thoracic and mediastinal disorders	Common	Respiratory arrest; respiratory depression
Gastrointestinal disorders	Common	Vomiting
Skin and subcutaneous disorders	Not known	Skin lesion; urticaria; skin reaction
Musculoskeletal and connective tissue disorders	Common	Muscle twitching
General disorders and administration site conditions	Common	Oedema; feeling hot; feeling cold

The following adverse reactions have been reported with the following contraindicated routes of administration:

Intrathecal/Epidural: Arachnoiditis, bowel/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizures, sensory disturbances, visual impairment including blindness, ocular and periocular inflammation, and residue or slough at injection site.

Intranasal: Allergic reactions, rhinitis, temporary/permanent visual impairment including blindness.

Ophthalmic: Increased intraocular pressure, infection, ocular and periocular inflammation including allergic reactions, residue or slough at injection site, temporary/permanent visual impairment including blindness.

Miscellaneous injection sites (*scalp, tonsillar fauces, sphenopalatine ganglion):* Blindness.

DRUG INTERACTIONS

Overview

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.

CYP3A4 INHIBITORS – Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration 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.

CYP3A4 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.

CYP3A4 SUBSTRATES – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected 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.

NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with methylprednisolone are described in the table below.

Drug Class or Type - DRUG or SUBSTANCE	**Interaction or Effect**
Aminoglutethimide	Aminoglutethimide may lead to a loss of corticosteroid-induced adrenal suppression.
Antibacterial -ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antibiotic -RIFAMPIN	CYP3A4 INDUCER

Drug Class or Type - DRUG or SUBSTANCE	Interaction or Effect
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects. 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.
Anticonvulsant - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (See WARNINGS AND PRECAUTIONS - Musculoskeletal, for additional information.) 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
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. Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATE)
Antitubercular drugs	Serum concentrations of isoniazid may be decreased.
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Aromatase inhibitor - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

Drug Class or Type - DRUG or SUBSTANCE	Interaction or Effect
Calcium Channel Blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Cholestyramine	Cholestyramine may increase the clearance of oral corticosteroids
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE) Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.
Digitalis glycosides	Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.
Immunosuppressant - CYCLOSPORINE	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of cyclosprine and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. 3) Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with concurrent use. Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone, therefore it is possible that adverse events associated with the individual use of either drug may be more apt to occur.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATE
Ketoconazole	Ketoconazole has been reported to significantly decrease the metabolism of certain corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITOR (and SUBSTRATE) Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose ASPIRIN (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels, which could lead to an increased risk of salicylate toxicity. 3) 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 concurrent use of corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Drug Class or Type - DRUG or SUBSTANCE	Interaction or Effect
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 is also an increased risk of hypokalemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.
Vaccines	Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or attenuated 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 AND PRECAUTIONS: Immune, Vaccinations).

Drug-Food Interactions
Grapefruit juice is a CYP3A4 inhibitor. See DRUG INTERACTIONS, CYP3A4 INHIBITORS above.

Drug-Laboratory Interactions
Corticosteroids may suppress reactions to skin tests.

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 discolouration 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:

Size of Joint	Examples	Range of Dosage (methylprednisolone acetate)
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 AND PRECAUTIONS).

OVERDOSAGE

Methyprednisolone
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 corticosteroid may be reduced only temporarily.

In the event of overdosage, no specific antidote is available.

Methylprednisolone is dialyzable.

Lidocaine
Overdose with lidocaine can manifest itself in a transient stimulation of the central nervous system with early symptoms: yawning, restlessness, dizziness, nausea, vomiting, dysarthria, ataxia, hearing and visual disturbances. With moderate intoxication also twitching and convulsions can occur. This can be followed by unconsciousness, respiratory depression and coma. In very severe intoxication due to decreased myocardial contractility and delayed impulse conduction, hypotension and cardiovascular collapse can be expected to be followed by a complete heart block and cardiac arrest; treatment will be symptomatic. Convulsions may be treated with diazepam.Ventilation for respiratory depression. Hypotension can be treated by the administration of fluids and dopamine. With asystole, adrenaline administration and, if necessary, a pacemaker insertion.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylprednisolone

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

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.

Pharmacokinetics

No pharmacokinetic studies have been performed with the combination product of methylprednisolone and lidocaine, however, data are provided from pharmacokinetic studies performed with the individual product components methylprednisolone and lidocaine.

Absorption:

Methylprednisolone:
One in-house study of eight volunteers determined the pharmacokinetics of a single 40 mg intramuscular dose of DEPO-MEDROL. The average of the individual peak plasma concentrations was 14.8 ± 8.6 ng/mL, the average of the individual peak times (t_{max}) 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).

Lidocaine:
Pharmacokinetics of lidocaine after synovial absorption following intra-articular bolus injection in patients with knee joint arthroscopy was studied with different maximum concentration (C_{max}) values reported. The C_{max} values are 2.18 µg/mL at 1 hour (serum) and 0.63 µg/mL at 0.5 hour (plasma) following administration of lidocaine doses of 7 mg/kg and 400 mg, respectively. Other reported serum Cmax values are 0.69 µg/mL at 5 minutes and 0.278 µg/mL at 2 hours following administration of lidocaine doses of 25 mL of 1% and 20 mL of 1.5%, respectively.

Pharmacokinetic data of lidocaine after intra-bursa and intra-cyst administrations for local effect are not available.

Distribution:

Methylprednisolone:
Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4 L/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.

Lidocaine:
The plasma protein binding of lidocaine is concentration-dependent, and binding decreases as concentration increases. At concentrations of 1 to 5 µg/mL, 60%-80% lidocaine is protein bound. Binding is also dependent on the plasma concentration of the α1-acid glycoprotein.

Lidocaine has a volume of distribution at steady state of 91 L.

Lidocaine readily crosses the placenta, and equilibrium of unbound drug concentration is rapidly reached. The degree of plasma protein binding in the fetus is less than in the mother, which results in lower total plasma concentrations in the fetus.

Metabolism:

Methylprednisolone:
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 drug interactions based on CYP3A4-mediated metabolism, see DRUG INTERACTIONS).

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 modulated by P-gp.

Lidocaine:
Lidocaine is mainly metabolized by the liver. The main metabolites of lidocaine are monoethylglycine xylidide, glycinexylidide, 2,6-dimethylaniline, and 4-hydroxy-2,6-dimethylaniline. The lidocaine N-dealkylation to monoethylglycine xylidide is considered to be mediated by both CYP1A2 and CYP3A4. The metabolite 2,6-dimethylaniline is converted to 4-hydroxy-2,6-dimethylaniline by CYP2A6 and CYP2E1.

Excretion:

Methylprednisolone:
The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6 mL/min/kg.

Lidocaine:
The clearance of lidocaine in plasma following intravenous bolus administration is 9 to 10 mL/min/kg.

The elimination half life of lidocaine following intravenous bolus injection is typically 1.5 to 2 hours.

The pharmacological actions of monoethylglycine xylidide and glycinexylidide are similar to but less potent than those of lidocaine. Monoethylglycine xylidide has a half life of approximately 2.3 hours and glycinexylidide has a half life of about 10 hours and may accumulate after long-term administration.

Only 3% of lidocaine is excreted unchanged by the kidneys. About 73% of lidocaine appears in the urine as 4-hydorxy-2,6-dimethylaniline metabolite.

Special Population

Methylprednisolone:
No pharmacokinetic studies have been performed for methylprednisolone in special populations.

Special Population

Lidocaine:

Hepatic impairment

Following intravenous administration, the half life of lidocaine has approximately 3-fold increase in patients with liver impairment. Pharmacokinetic data of lidocaine after intra-articular, intra-bursa and intra-cyst administrations for local effect are not available in hepatic impairment.

Renal impairment

Mild to moderate renal impairment (CLcr 30-60 mL/min) does not affect lidocaine pharmacokinetics but may increase the accumulation of glycinexylidide metabolite following intravenous administration. However, lidocaine clearance decreases about half and its half life is approximately doubled with increased accumulation of glycinexylidide metabolite in patients with severe renal impairment (Clcr <30 mL/min).

The pharmacokinetics of lidocaine and its main metabolite of monoethylglycine xylidide are not altered significantly in haemodialysis patients who receive an intravenous dose of lidocaine.

Pharmacokinetic data of lidocaine after intra-articular, intra-bursa and intra-cyst administrations for local effect are not available in renal impairment.

STORAGE AND STABILITY

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

SPECIAL HANDLING INSTRUCTIONS

See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, General

DOSAGE FORMS, COMPOSITION AND PACKAGING

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.
Each mL of this preparation contains:

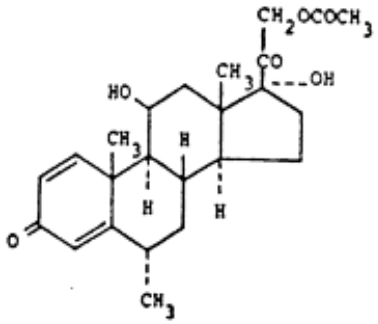
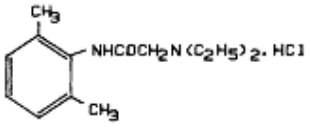
methylprednisolone acetate USP	40.0 mg
lidocaine HCl USP	10.0 mg
polyethylene glycol 3350 NF	29.1 mg
benzyl alcohol NF	9.2 mg
sodium chloride	6.6 mg
myristyl-gamma-picolinium chloride	0.2 mg
water for injection	qs

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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

	DEPO-MEDROL	Lidocaine
Proper name:	sterile methylprednisolone acetate USP	lidocaine hydrochloride USP
Chemical name:	(1) Pregna-1,4-diene-3,20-dione,21 (acetyloxy)-11,17-di-hydroxy-6-methyl, (6∞, 11β-;(2)11β,17,21-trihydroxy-6∞-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:	$C_{24}H_{32}O_6$	$C_{14}H_{23}ClN_2O,H_2O$
Molecular Weight:	416.51	234.34
Physicochemical properties:	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.

TOXICOLOGY

Methylprednisolone

Based on conventional studies of safety pharmacology, repeated dose toxicity, 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.

Carcinogenesis: Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis: There was no evidence of a potential for genetic and chromosome mutations when tested in limited studies performed in bacterial and mammalian cells.

Reproductive toxicity: Corticosteroids have been shown to reduce fertility when administered to rats.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids such as methylprednisolone have been shown to induce malformations (cleft palate, skeletal malformations) and intra-uterine growth retardation.

Lidocaine

Carcinogenesis: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of lidocaine. In a carcinogenicity study in rats, the lidocaine metabolite 2,6-xylidine was administered in the diet to rats of both sexes before breeding, through pregnancy, and through the lactation period and to the male and female offspring through their lifetime at doses of 15, 50 and 150 mg/kg/day. Tumors in the nasal cavity, subcutaneous tumors and liver tumors were observed in the offspring at high doses. The clinical relevance of this finding is unknown.

Mutagenesis: Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine, 2,6-xylidine, showed weak genotoxic potential in vitro and in vivo.

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 analyzed for each gestation, as well as offspring development up to weaning. No effects could be detected.

Methylprednisolone plus Lidocaine

Carcinogenesis

Acute Toxicity: The LD_{50} 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.

Repeat-dose toxicity: 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.

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenesis: 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).

Local tolerance: 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.

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PART III: CONSUMER INFORMATION

PrDEPO-MEDROL WITH LIDOCAINE*
(sterile methylprednisolone acetate 40 mg/mL and lidocaine hydrochloride 10 mg/mL)

This leaflet is part III of a three-part "Product Monograph" published when DEPO-MEDROL with Lidocaine was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DEPO-MEDROL with Lidocaine. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DEPO-MEDROL with Lidocaine (methylprednisolone acetate and lidocaine hydrochloride) is used as an adjunctive treatment of acute or worsening (exacerbation) inflammation of joints and tendons. DEPO-MEDROL with Lidocaine is not a cure nor has any effect on the cause of the inflammation.

What it does:
DEPO-MEDROL with Lidocaine contains a corticosteroid hormone (glucocorticoid) and a local anaesthetic. It decreases the body's immune response to certain diseases and it helps to reduce pain and inflammation.

When it should not be used:
Do not take DEPO-MEDROL with Lidocaine if you have:

- allergic reaction to methylprednisolone acetate or any other steroid medicine or lidocaine or any similar local anaesthetics or any of the other ingredients in DEPO-MEDROL with Lidocaine; or
- any fungal infection or any untreated infections.
- viral diseases including vaccinia (cowpox), varicella (chicken pox), and herpes simplex of the eye.
- low platelet count.

DEPO-MEDROL with Lidocaine should not be given to premature infants because the formulation contains benzyl alcohol.

Patients taking DEPO-MEDROL with Lidocaine should not receive live vaccines.

What the medicinal ingredients are:
Methylprednisolone acetate and lidocaine hydrochloride.

What the nonmedicinal ingredients are:
Benzyl alcohol, myristyl-gamma-picolinium chloride, polyethylene glycol 3350 and sodium chloride.

What dosage forms it comes in:
1, 2 and 5 mL vials containing 40 mg/mL methylprednisolone acetate and 10 mg/mL lidocaine hydrochloride of suspension.

WARNINGS AND PRECAUTIONS

DEPO-MEDROL with Lidocaine is not to be injected into the vein (intravenous), or into the spinal cord (intrathecal).

Before taking DEPO-MEDROL with Lidocaine, talk to your doctor if you have:

- an infection (such as herpes simplex, chicken pox, tuberculosis, threadworm);
- bleeding problem, blood clotting problem;
- brittle bone (osteoporosis);
- high blood pressure;
- seizures (fits);
- thyroid problem (hypothyroidism);
- muscle pain or weakness (such as myasthenia gravis);
- skin cancer (Kaposi's sarcoma);
- heart problems such as heart failure;
- certain eye diseases such as glaucoma, cataracts; herpes infection;
- kidney disease;
- liver disease such as cirrhosis;
- certain mental or mood conditions (such as depression);
- stomach or gut problems (ulcer, ulcerative colitis);
- low potassium or calcium;
- Cushing's disease (caused by an excess of cortisol hormone);
- weak immune response;
- high blood sugar.

Before you have any operation, tell your doctor, dentist or anesthetist that you are taking DEPO-MEDROL with Lidocaine.

Pregnancy and breast feeding
You must tell your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant as this medicine could slow the baby's growth.

You should also tell your doctor if you are breast feeding as small amounts of corticosteroid medicines may get into breast milk. It is not known whether Lidocaine can get into breast milk.

Children:
Corticosteroids can affect growth in children.
DEPO-MEDROL with Lidocaine contains benzyl alcohol and is not recommended to be used in infants since benzyl alcohol has been reported to cause "gasping syndrome" that may result in death.

INTERACTIONS WITH THIS MEDICATION

Before taking DEPO-MEDROL with Lidocaine talk to your doctor about all your other medications, including those you bought without prescription, herbal or natural products. Especially if you are taking the following:

- drugs to treat glaucoma and epilepsy such as acetazolamide
- drugs to prevent or alleviate nausea and vomiting such as aprepitant or fosaprepitant
- drugs to treat cancer such as aminoglutethimide or cyclophosphamide
- drugs to "thin" the blood; anticoagulants such as acenocoumarol, phenindione and warfarin
- drugs to treat myasthenia gravis (a muscle condition) such as distigmine and neostigmine
- antibiotics and antifungals (such as ketoconazole, itraconazole amphotericin B, erythromycin, clarithromycin, troleandomycin, rifampicin and rifabutin)
- aspirin and non-steroidal anti-inflammatory medicines (also called NSAIDs) such as ibuprofen
- drugs to treat epilepsy such as barbiturates, carbamazepine, phenytoin and primidone
- drugs for heartburn and acid indigestion such as cimetidine
- cyclosporine
- drugs for heart problems or high blood pressure such as calcium channel blockers, digoxin and diltiazem
- water pills (diuretics)
- hormone replacement therapy or hormonal oral contraceptives
- drugs to treat HIV infections such as indinavir or ritonavir
- pancuronium or vercuronium – or other medicines called neuromuscular blocking agents which are used in some surgical procedures
- tacrolimus – used following an organ transplant to prevent rejection of the organ
- vaccines – tell your doctor or nurse if you have recently had, or are about to have any vaccination
- drugs to treat diabetes
- drugs to treat tuberculosis
- drugs to treat high cholesterol (cholestyramine)
- aromatase inhibitors (drugs to treat breast or ovarian cancer)
- immunosuppressants (drugs that suppress or reduce the strength of the body's immune system

Do not drink grapefruit juice while taking DEPO-MEDROL with Lidocaine.

Driving and Using Machines
Side effects, such as dizziness, vertigo, visual disturbance and fatigue are possible after treatment with corticosteroids. If you experience these effects, you should not drive or operate machinery.

PROPER USE OF THIS MEDICATION

DEPO-MEDROL with Lidocaine is to be given to you as an injection into the joint (intra-articular or intra-synovial, peri-articular and intrabursal injection) or the tendon (intratendinous or intra-ganglion injection) by your health care provider. The dose of DEPO-MEDROL with Lidocaine is depending on your condition and how severe it is.
When your condition has improved, your dose will be reduced gradually. DEPO-MEDROL with Lidocaine should not be stopped abruptly.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, DEPO-MEDROL with Lidocaine can have side effects although not everybody gets them.

DEPO-MEDROL with Lidocaine may hide symptoms of infections, may cause latent infections to become active, and may induce infections by normally inoffensive organisms due to lowered body resistance.

Potential side effects with DEPO-MEDROL with Lidocaine include:

Allergic Reactions:
- anaphylaxis (a severe, life-threatening allergic reaction)
- cardiac arrest
- bronchospasm (narrowing of the airway)
- trouble breathing

Cardiovascular:
- heart failure
- heart attack
- arrhythmia (irregular heartbeat)
- bradycardia (slow heartbeat)
- high and low blood pressure
- blood clots
- thrombophlebitis (vein inflammation)

Dermatologic:
- thin fragile skin
- impaired wound healing
- swelling
- ecchymosis (spots caused by ruptured blood vessels)
- petechiae (reddish spot containing blood that appears in skin)
- stretch marks

- dry, scaly skin
- rash
- redness
- itching
- acne
- increased sweating
- injection site reaction
- lightening or darkening of an area of skin
- abscess
- suppressed reaction to skin tests
- thinning hair

Endocrine and Metabolism:
- development of Cushingoid state (abnormal bodily condition caused by excess corticosteroids)
- moon face (enlargement of chin and forehead)
- weight gain
- abnormal fat deposits
- suppression of pituitary-adrenal axis (a condition that could lead to disabling the body's responses to physiological stress such as severe infections or trauma)
- suppression of growth in children
- abnormal hair growth
- new symptoms of diabetes

Gastrointestinal:
- stomach ulcer
- stomach bleeding
- inflammation of the pancreas and esophagus
- perforation of the bowel
- nausea
- vomiting or altered sense of taste (with rapid administration of large doses)
- abdominal pain
- bloating
- diarrhea
- indigestion
- bowl/bladder dysfunction
- increased appetite

Hematology:
- Above normal white blood cell count

Hepatic:
- enlarged liver

Musculoskeletal:
- loss of muscle mass
- muscle weakness
- muscle pain
- malaise (feeling of general discomfort or uneasiness)
- osteoporosis
- pathological fractures
- vertebral compression fractures
- tendon rupture, (particularly of the Achilles tendon)
- Charcot joint disease (neuropathic arthropathy)
- pain and inflammation of the tissues surrounding the injection site
- joint pain

Neurologic:
- seizures
- headache
- vertigo
- pain and tenderness
- impaired sensation, strength, and reflexes
- sensation of tingling, tickling, prickling, or burning of a person's skin
- sensation of heat, cold, numbness
- twitching
- light-headedness
- dizziness
- drowsiness
- ringing in the ears
- tremors
- fainting
- amnesia
- dizziness

Ophthalmologic:
- cataracts
- increased intraocular pressure
- glaucoma
- bulging of the eye
- blurred or double vision
- blindness

Psychiatric:
- depression
- emotional instability
- euphoria (intense feelings of well-being, elation, happiness, excitement and joy)
- insomnia
- mood swings
- personality changes
- nervousness
- apprehension
- confusion
- thoughts of suicide
- delusion
- hallucination
- confusion
- schizophrenia
- anxiety

Sexual Function/Reproduction:
- menstrual irregularities
- increased or decreased motility and number of sperm

Other:
- hiccups, fatigue, irritability

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Seek IMMEDIATE medical attention**
	Only if severe	**In all cases**	
Burst or bleeding ulcers: symptoms of which are stomach pain, bleeding from the back passage, black or bloodstained stools and/or vomiting blood			√
Flare up of a previous TB* : symptoms of which could be coughing blood or pain in the chest			√
Serious allergic reaction: symptoms of which include rash, itching/swelling (especially of the face/tongue/throat), severe dizziness and trouble breathing			√
Signs of infection (such as persistent fever/cough/sore throat, painful urination, eye pain/discharge)		√	
High blood pressure (symptoms of which are headaches or generally feeling unwell)		√	
Fast/pounding/irregular heartbeat		√	
Swelling		√	
Cramps and spasms		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Seek IMMEDIATE medical attention**
	Only if severe	**In all cases**	
Vision changes		√	
Increased thirst/urination		√	
Mental/mood changes (such as mood swings, depression, suicidal thinking, agitation, anxiety)		√	
Tendon pain			√
Bone/joint pain			√
Easy bruising/bleeding			√
Pain/redness/swelling at the injection site	√		
Thinning skin	√		
Poor wound healing	√		
Unusual hair growth	√		
Unusual skin growth		√	

This is not a complete list of side effects. For any unexpected effects while taking DEPO-MEDROL with Lidocaine, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C and 30°C. Protect from freezing. Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001.

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