DATA SHEET

Depo-Medrol® with Lidocaine

Methylprednisolone acetate, lignocaine hydrochloride injection.

PRESENTATION

Depo-Medrol with Lidocaine is a white aqueous suspension containing methylprednisolone acetate 40 mg/mL and lignocaine hydrochloride 10 mg/mL in 1 mL vials.

USES

Actions

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 (oedema, fibrin deposition, capillary dilation, 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 cicatrisation).

These compounds inhibit inflammatory response whether the inciting agent is mechanical, chemical or immunological.

Lidocaine is a potent local anaesthetic 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 anaesthetic influences the permeability of the membrane is unknown. As general rule, small nerve fibres are more susceptible to the action of local anaesthetics than are large fibres.

Pharmacokinetics

Absorption

Time-to peak concentrations (Tmax) are 7.3 ± 1 hour after I.M. and 4 - 8 hours after I.A. administration.

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.

After a single intramuscular injection of 40 to 80mg methylprednisolone acetate, duration of HPA axis suppression ranged from four to eight days.

After intra-articular administration methylprednisolone acetate diffuses from the joint into systemic circulation over approximately 7 days.

Distribution

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.

Biotransformation or Metabolism

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-6alpha-methylprednisone. The metabolites are excreted in the urine as glucuronides, sulphates and unconjugated compounds. These conjugation reactions occur principally in the liver and to some extent in the kidney.

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

Indications

Depo-Medrol with Lidocaine by intra-synovial of soft tissue administration (including periarticular and intrabursal) 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 gouty arthritis
- Epicondylitis
- Acute nonspecific tenosynovitis
- Post-traumatic osteoarthritis
- Acute and subacute bursitis
- Depo-Medrol with Lidocaine may also be useful in cystic tumours of an aponeurosis or tendon (ganglia).

DOSAGE AND ADMINISTRATION

Because of possible physical incompatibilities, Depo-Medrol with Lidocaine Sterile Aqueous Suspension (methylprednisolone acetate) 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.

When multidose vials are used, special care to prevent contamination of the contents is essential (see **Warnings and Precautions**).

Because complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

The lowest possible dose of corticosteroid should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual.

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 steroid has no effect on the cause of the inflammation.

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
Large	Knees, Ankles, Shoulders	20-80mg
Medium	Elbows, Wrists	10-40mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4-10mg

Procedure: It is recommended that the anatomy of the joint involved by 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 the 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 the 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 orthopaedic correction should be employed.

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

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.

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, the 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 form 4 to 30mg. In recurrent or chronic conditions, repeated injections may be necessary.

CONTRAINDICATIONS

Depo-Medrol with lidocaine is contraindicated

- in patients who have systemic infections unless specific anti-infective therapy is given

- in patients with known hypersensitivity to Methylprednisolone or components of Depo-Medrol with Lidocaine.
- in patients with known hypersensitivity to Lidocaine or other anaesthetics of the amide type
- for use by intravenous, intrathecal injection or any other unspecified route of administration.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see **Warnings and Precautions**)

WARNINGS AND PRECAUTIONS

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.

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

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

Sterile technique is necessary to prevent infections or contamination.

Multidose use of Depo-Medrol 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. Multidose use of Depo-Medrol from vials is not recommended for intrasynovial injection.

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.

Immunosuppressive Effects/Increased Susceptibility to Infections

Due to their suppression of the inflammatory response and immune function, corticosteroids may increase susceptibility to fungal, bacterial and viral infection and their severity. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, they should seek urgent medical attention. Passive immunisation is recommended if non-immune patients who come into contact with chicken pox. If a diagnosis of chicken pox is confirmed the illness warrants specialist care and urgent treatment.

The immunosuppressive effects of corticosteroids may also result in activation of latent infection or exacerbation of existing infection. Corticosteroids should be used with great care in patients with known or suspected parasitic infections such as Strongyloides infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicaemia.

It is also important to note that cortiocsteroids may also mask some signs of infection which may reach an advanced stage before the infection is recognised.

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. Therefore caution must be exercised in patients with AIDS/HIV or diabetes.

Depo-Medrol with lidaocaine is not recommended for use in patients with septic shock or sepsis syndrome. The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended and a systematic review concluded that short-course, high-dose corticosteroids did not support their use. However, meta-analyses and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in those with vasopressor-dependent septic shock.

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.

The use of methylprednisolone 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.

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

Blood and Lymphatic System

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids.

Hypersensitvity reactions

Allergic reactions (e.g. angioedema) may occur.

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

Endocrine

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.

Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

It is important to note that acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

Drug-induced adrenocortical insufficiency may be minimised by gradual reduction of dosage, however, symptoms may persist for months after discontinuation of therapy;.

In patients on corticosteroid therapy (or those who have discontinued treatment but continue to experience symptoms of adrenal insufficiency) who are subjected to unusal sress such as intercurrent illness, trauma or surgery, increased dosage (or reinstitution) of rapidly acting corticosteroids nmay be required. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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

Corticosteroids should be used with caution in patients with hypothyroidism as there is potential for an enhanced effect of corticosteroids on patients in these patients.

Metabolism and Nutrition

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes and predisposes those on long term corticosteroid therapy to diabetes mellitus. Therefore, corticosteroids should be used with caution in patients with or a family history of diabetes mellitus.

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. Therefore, particular carre is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders.

Symptoms of potentially severe psychiatric adverse reactions associated with corticosteroid use 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

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

Corticosteroids should be used with caution in patients with myasthenia gravis

Ocular

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible risk of corneal scarring, loss of vision and corneal perforation.

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.

Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

Cardiovascular

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

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal

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 haemorrhage 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, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary

Corticosteroids should be used with caution in patients with hepatic failure.

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

Musculoskeletal

Corticosteroids should be used with caution in patients with myasthenia gravis who are receiving anticholinesterase therapy as corticosteroid use may decrease plasma anticholinesterase activity. 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.

Corticosteroids hosuld be used with caution in patients with osteoporosis. Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Corticosteroid should be used with caution in patients with Duchenne's muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous activities.

Corticosteroids should be used with caution in patients with previous steroid myopathy.

Renal and Urinary

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.

Discontinuation

A steroid "withdrawal syndrome", seemingly unrelated to adrenocortical insufficiency, may occur following abrupt discontinuance of glucocorticoids. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels (see **Adverse Events**, **General disorders and administration site conditions)**

Injury, Poisoning and Procedural Complications

High doses of systemic corticosteroids should not be used for the treatment of traumatic brain injury.

While crystals of adrenal steroids in the dermis suppress inflammatory reaction, 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. 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.

Other

Because complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

The lowest possible dose of corticosteroid should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual.

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. 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. 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.

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 deterioration.

Because rare instances of anaphylactic reactions have occurred in patients receiving parenteral corticosteroid 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 in the formulation. Rarely has skin testing demonstrated a reaction to methylprednisolone acetate, per se.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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

Use in preganacyand Lactation

Pregnancy

Some animal studies have shown the corticosteroids, when administered to the mother at high doses, may cause foetal 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 childbearing potential requires that the benefits of the drug be carefully weighed against the potential risk to the mother and embryo or foetus. 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. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. There are no known effects of corticosteroids on labour and delivery. The use of local anaesthetics such as Lidocaine during labour and delivery may be associated with adverse effects on mother and foetus.

Lactation

Corticosteroids are excreted in breast milk. It is not known whether lidocaine is excreted in human breast milk. The potential benefits of treatment must therefore be weighed against the possible hazards to the infant.

Use in children

Growth and development of infants and children receiving long-term, daily-divided dose glucocorticoid therapy should be carefully observed. Corticosteroids cause growth retardation in infancy, childhood and adolescence. The use of such a regimen should be restricted to those most serious indications. Use in children should be limited to the shortest possible time.

Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri) has been reported, usually after treatment withdrawal of methylprednisolone.

Use in the Elderly

The use of corticosteroids, particualry long-term use, in the elderly should be planned bearing in mind the more serious consequences of the common side effects, especially, osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

ADVERSE EFFECTS

Note the following are typical for all systemic steroids. Their inclusion in this list does not necessarily indicate that the specific event has been observed with this particular formulation.

Vascular disorders	Hypertension Hypotension
Cardiac disorders	Heart failure congestive (in susceptible patients)
Musculoskeletal disorders	Arthralgia Growth retardation Muscle atrophy Muscle weakness Myalgia Steroid myopathy

	Osteoporosis Neuropathic arthropathy Avascularc osteonecrosis Pathologic fractures,
Gastrointestional disorders	Abdominal distension Abdominal pain Diarrhoea Dyspepsia Nausea Peptic ulcer with possible subsequent perforation and haemorrhage Oesophagititis Gastric haemorrhage Intestinal erforation Pancreatitis Oesophagitis ulcerative Oesophagitis candidiasis
Investigations	Alanine transaminase increased Aspartate transaminase increased Blood alkaline phosphatise increased Blood potassium decreased Carbohydrate tolerance decreased Increased calcium excretion/unrine calcium increased
Skin and subcutaneous disorders	Impaired wound healing, Angioedema Thin fragile skin Petechiae Ecchymosis Erythema Hirsutism Hyperhidrosis Pruritus Rash Skin atrophy Skin striae Urticaria Acne Telangiectasia
Psychiatric disorders	Abnormal behaviour Affective disorder (including affect lability, depressed mood, euphoric mood, psychological dependence, suicidal ideation) Behavioural disturbances (including anxiety, confusional state, insomnia, irritability) Mental disorder Mood swings Personality change Psychotic behaviour Psychotic disorders (including mania, delusion,

	hallucination and schizophrenia [aggravation of])
Nervous system disorders	Amnesia Cognitive disorder Convulsions Dizziness Headache Intracranial pressure increased (with papilloedema [benign intracranial hypertension])
Endocrine disorders	Development of cushingoid state, suppression of hypothalamo-pituitary-adrenal axis, manifestations of latent diabetes mellitus, suppression of growth in infants, children and adolescents.
Eye disorders	Posterior subcapsular cataracts, increased intraocular pressure, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease
Reproductive system and breast disorders	Menstruation irregularities and amenorrhoea
Metabolic and Nutritional disorders	Sodium retention Fluid retention Alkalosis hypokalaemic Carbohydrate tolerance decreased Increased appetite (which may result in weight gain), Increased requirements for insulin or oral hypoglycaemic agents in diabetics Metabolic acidosis Negative nitrogen balance due to protein catabolism
Eye disorders	Cataract subcapsular Glaucoma Exophthalmos Intraocular pressure increased Corneal or scleral thinning Exacerbation of ophthalmic viral or fungal disease
Ear and labyrinth disorders	Vertigo
Infections and Infestations	Increased susceptibility to and severity of infection with suppression of clinical symptoms and signs Opportunistic infections Recurrence of dormant tuberculosis
Immune system disorders	Hypersensitivity reactions including anaphylaxis may suppress reactions to skin tests
General disorders and administration site conditions	Fatigue Impaired healing Malaise Leucocytosis 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.
Injury, poisoning and procedural complications	Long bone and spinal compression fracture Tendon rupture (particularly of the Achilles tendon)

LIDOCAINE

Nervous disorders	Lightheadedness Nervousness Apprehension Euphoria Confusion Dizziness Vomiting Sensation of heat Cold Numbness Twitching Tremors Convulsions Loss of consciousness Drowsiness Tinnitus Blurred or double vision Respiratory depression Respiratory arrest
Cardiac disorders	Bradycardia Cardiovascular collapse Hypotension Cardiac arrest
Allergic reactions	Cutaneous lesions Urticaria Oedema Anaphylactic reactions

INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important.

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is metabolized mainly by the CYP3A4 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, resulting in increased plasma concentration of methylprednisolone. These include:

- Antifungals such as ketoconazole and itraconazole
- Antiemetics, such as aprepitant and fosaprepitant
- Immunosuppressants such as cyclosporine
- Macrolide antibacterials such as clarithromycin, erythromycin and troleanomycin
- HIV-Protease inhibitors
- Ciclosporin
- Ritonavir
- Diltiazem
- Grapefruit juice

Coadministration of CYP3A4 inhibitors may require titration of methylprednisolone dosage to reduce the risk of adverse effects and avoid steroid toxicity.

CYP3A4 INDUCERS

Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentrations of methylprednisolone. These include:

- Phenobarbital
- Phenytoin
- Rifampicin
- Rifabutin
- Carbamazepine
- Primidone
- Aminogluethimide

Coadministration of these substances 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 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.

OTHER INTERACTIONS

Other interactions and effects that occur with methylprednisolone are described below.

Antacids

Concurrent use may decrease absorption of corticosteroids. Efficacy may be reduced sufficiently to require dosage adjustments in patients receiving small doses of corticosteroids.

Antidiabetic agents

Corticosteroids may increase blood glucose levels. Dose adjustments of antidiabetic therapy may be required with concurrent therapy.

Oral anticoagulants

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 (such as INR or prothrombin time) should be monitored to maintain the desired anticoagulant effects.

Anticholinergics

Corticosteroids may influence the effect of anticholinergics.

Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs.

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.

Cardiac glycosides

There is a risk of toxicity if hypokalaemia occurs due to corticosteroid treatment.

Oral contraceptives

Oral contraceptives retard the metabolism of corticosteroids due to increased binding to globulin, resulting in increased plasma levels of corticosteroids and potentiating their biological effect. The dose of corticosteroids may need to be adjusted when commencing or stopping oral contraceptive therapy.

Diuretics

Excessive potassium loss maybe experienced with concurrent use of corticosteroids and potassium depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide).

Mifepristone

The effect of corticosteroids may be reduced for 3-4 days after taking mifepristone.

NSAIDs

Concomitant administration may increase the risk of gastrointestinal bleeding and ulceration.

Methylprednisolone may increase the renal clearance of aspirin. This resulting decrease in salicylate serum levels could lead to an increased risk of salicylate toxicity when methylprednisolone is withdrawn.

Somatropic

Concomitant administration may inhibit the growth promoting effect of somatropin.

Sympathomimetics

There is an increased risk of hypokalaemia with concurrent high doses of corticosteroids and sympathomimetics such as salbutamol, salmeterol, terbutaline or formoterol.

Antivirals

Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.

Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.

Antifungals

The risk of hypokalaemia may be increased with amphotericin.

Vaccines

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

OVERDOSAGE

There is no clinical syndrome of acute overdosage with Depo-Medrol with lidocaine (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.

PHARMACEUTICAL PRECAUTIONS

Shelf life

24 months

Storage condition

Store below 25ºC. Protect from freezing.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

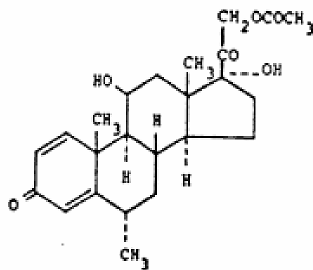
Depo-Medrol with Lidocaine is available in vials of 1 mL.

FURTHER INFORMATION

The chemical name for methylprednisolone acetate is pregna-1,4-diene-3,20-dione, 21-(acetyloxy)-11,17-dihydroxy-6-methyl-,(6 α ,11ß). The chemical name for lignocaine hydrochloride is 2-(Diethylamino)-N-(2,6-dimethylphenyl)-acetamide hydrochloride.

Strutural formula:

Methylprednisoone acetate



Lignocaine hydrochloride

Molecular formula: $C_{24}H_{32}O_6$ | $C_{14}H_{22}N_2O,HCl$

Molecular weight: 416.51 | 234.34

Depo-Medrol with Lidocaine contains myristyl-gamma-picolinium chloride 0.19 mg/mL and benzyl alcohol 8.7 mg/mL as preservatives.

NAME AND ADDRESS

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DATE OF PREPARATION

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Depo-Medrol is a registered trademark of Pfizer Inc.