DEPO-MEDROL® WITH LIDOCAINE

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEPO-MEDROL® WITH LIDOCAINE.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolone acetate with lidocaine (as hydrochloride): (40 mg, 10 mg)/ml,

Methyprednisolone 4%, Lidocaine Hydrochloride 1%

Excipients with known effect:
Benzyl alcohol: 8.7 mg per ml.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Suspension for Injection.
White, sterile aqueous suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Depo-Medrol may be used by any of the following routes: Intra-articular, Intrabursal, Intrasynovial Cyst and Tendon Sheath injection.
It must not be used by the intrathecal or intravenous routes (see section 4.3 **Contraindications**)
The following routes of administration are not recommended; epidural, intranasal, intraocular and any other unapproved route of administration (see section 4.4 **Special Warnings and Precautions for Use)**

Methylprednisolone acetate with lidocaine 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

4.2 Posology and Method of Administration

Because of possible physical incompatibilities, methylprednisolone acetate with lidocaine should not be diluted or mixed with other solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

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

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:

Table 1.General guide for dosage

Size of Joint	Example	Range of Dosage
Large	Knees Ankles Shoulders	20-80 mg
Medium	Elbows Wrists	10-40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4-10 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 methylprednisolone acetate 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 orthopedic correction should be employed.

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.

If a local anesthetic is used prior to injection of methylprednisolone acetate 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.

Depo-Medrol with Lidocaine vials are intended for single dose use only. (see section 4.4 **Special warnings and precautions for use**).

4.3 Contraindications

Depo-Medrol with Lidocaine is contraindicated:

- in patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- in patients with known hypersensitivity to other local anaesthetics of the amide type
- in patients who have systemic infection unless specific anti-infective therapy is employed
- for use by the intrathecal route (due to its potential for neurotoxicity, see section 4.8)
- for use by the intravenous route

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the minimum period. Frequent patient review is required to appropriately titrate the dose against disease activity (see section 4.2).

Depo-Medrol with Lidocaine vials are intended for single dose use only.
Any multidose use of the product may lead to contamination.

Depo-Medrol with Lidocaine is not recommended for intranasal, intra-ocular, or any other unapproved route of administration.

Severe medical events have been reported in association with the intrathecal/epidural routes of administration (see section 4.8). Appropriate measures must be taken to avoid intravascular injection.

Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with Depo-Medrol with Lidocaine.

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

Systemic absorption of methylprednisolone occurs following intra-articular injection of Depo-Medrol with Lidocaine. Systemic as well as local effects can therefore be expected.

Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. In patients who have received more than physiological doses of systemic corticosteroids (approximately 6 mg methylprednisolone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 6 mg methylprednisolone is reached, dose reduction should be slower to allow the HPA-axis to recover.

The following precautions apply for parenteral corticosteroids:
Following intra-articular injection, the occurrence of 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.

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.

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

Intra-articular corticosteroids are associated with a substantially increased risk of inflammatory response in the joint, particularly bacterial infection introduced with the injection. Charcot-like arthropathies have been reported particularly after repeated injections. Appropriate examination of any joint fluid present is necessary to exclude any bacterial infection, prior to injection.

Corticosteroids should not be injected into unstable joints.

Sterile technique is necessary to prevent infections or contamination.
Immunosuppressant Effects/Increased Susceptibility to Infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised.

With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

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

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.

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. A systematic review of 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 patients with vasopressor-dependent septic shock.

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

Endocrine Effects
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.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 32 mg daily of methylprednisolone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 32 mg daily of methylprednisolone.
- Patients repeatedly taking doses in the evening.

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

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.

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

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

Metabolism and Nutrition

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

Psychiatric Effects

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Nervous System Effects

Corticosteroids should be used with caution in patients with seizure disorders.
Corticosteroids should be used with caution in patients with myasthenia gravis (also see myopathy statement in Musculoskeletal Effects section).

There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

Ocular Effects

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids. Central serous chorioretinopathy, may lead to retinal detachment.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Corticosteroids should be used cautiously in patients with ocular herpes simplex, because of possible corneal perforation.

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

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

Vascular Effects
Corticosteroids should be used with caution in patients with hypertension.

Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

Gastrointestinal Effects
High doses of corticosteroids may produce acute pancreatitis.

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.

Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis.

In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

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

Hepatobiliary Effects
Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore appropriate monitoring is required.

Drug induced liver injury including acute hepatitis or liver enzyme increase can result from cyclical pulsed IV methylprednisolone (usually at initial dose $\geq$ 1 g / day). Rare cases of hepatotoxicity have been reported. The time to onset can be several weeks or longer. In the majority of case reports resolution of the adverse events has been observed after treatment was discontinued.

Corticosteroids should be used with caution in patients with liver failure or cirrhosis.

Musculoskeletal Effects
An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g. myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (e.g. pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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

Renal and Urinary Disorders
Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

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

Injury, Poisoning and Procedural Complications
Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury, a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

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.

Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8).

Other
Corticosteroids should be used with caution in patients with a predisposition to thrombophlebitis.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects (see section 4.5).

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

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

Paediatric population

Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Treatment should be limited to the minimum dosage for the shortest possible time. The use of such a regimen should be restricted to those most serious indications.
Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Excipient Information

Benzyl alcohol

Depo-Medrol with Lidocaine contains benzyl alcohol (see section 2). The preservative benzyl alcohol may cause hypersensitivity reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in paediatric patients including neonates ("gasping syndrome"). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol containing formulations should only be used in neonates if it is necessary and if there are no alternatives possible. Premature and low-birth weight neonates may be more likely to develop toxicity. Benzyl alcohol containing formulations should not be used for more than 1 week in children under 3 years of age unless necessary. It is important to consider the total quantity of benzyl alcohol received from all sources, and high volumes should be used with caution and only if necessary, especially in patients with liver or kidney impairment, as well as in pregnant or breast-feeding women, because of the risk of accumulation and toxicity (metabolic acidosis).

Sodium
Depo-Medrol with Lidocaine contains less than 1 mmol sodium (23 mg) in each vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

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. Co-administration 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 co-administration.

1. Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin (CYP3A4 inhibitor and substrate). Since concurrent administration of these agents results in a mutual inhibition of metabolism (which may increase the plasma concentrations of either or both drugs), it is possible that convulsions and other adverse effects associated with the individual use of either drug may be more apt to occur.

2. Drugs that induce hepatic enzymes, such as rifampicin (antibiotic CYP3A4 inducer), rifabutin, carbamazepine (anticonvulsant CYP3A4 inducer and substrate), phenobarbitone and phenytoin (anticonvulsants CYP3A4 inducers), primidone, and aminoglutethimide (aromatase inhibitor) enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Aminoglutethimide- induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

3. Antibiotics/Antimycotics - Drugs such as erythromycin (macrolide antibacterial CYP3A4 inhibitor and substrate), itraconazole and ketoconazole antifungal CYP3A4 inhibitors and substrates) may inhibit the metabolism of corticosteroids and thus decrease their clearance.
Troleandomycin (CYP3A4 inhibitor), as well as clarithromycin, erythromycin, itraconazole and ketoconazole (CYP3A4 inhibitors and substrates) increase the effects and the side effects of methylprednisolone.

The acetylation rate and clearance of isoniazid (CYP3A4 inhibitor), an antibacterial drug, can be increased by methylprednisolone.

4. Steroids may reduce the effects of anticholinesterases in myasthenia gravis.

An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs (see section 4.4).

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.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

5. The effect of methylprednisolone on oral anticoagulants is variable. The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding and to maintain the desired anticoagulant effects.
There are also reports of diminished effects of anticoagulants when given concurrently with corticosteroids.

6. There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.

7. Antidiabetics - Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

8. Antiemetics - Aprepitant and fosaprepitant (CYP3A4 inhibitors and substrates).

9. Antivirals - HIV protease inhibitors: Indinavir, ritonavir and pharmacokinetic enhancers (cobicistat) (CYP3A4 inhibitors and substrates) may increase plasma concentrations of corticosteroids. Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.

10. Calcium channel blocker - Diltiazem (CYP3A4 inhibitor and substrate).

11. Contraceptives (oral) - Ethinylestradiol/norethindrone (CYP3A4 inhibitors and substrate).

12. Other immunosuppressants like cyclophosphamide and tacrolimus are substrates of CYP3A4.

13. Potassium-depleting agents - When corticosteroids are administered concomitantly with potassium-depleting agents (i.e. diuretics), patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists.

14. Grapefruit juice - CYP3A4 inhibitor.

4.6 Fertility, pregnancy and lactation

Fertility
Corticosteroids have been shown to impair fertility in animal studies (see section 5.3).

Pregnancy
Methylprednisolone
The ability of corticosteroids to cross the placenta varies between individual drugs, however, methylprednisolone does cross the placenta. One retrospective study found an increased incidence of low birth weights in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. Although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids, those exposed to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women.

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

Lidocaine
The use of local anaesthetics such as lidocaine during labour and delivery may be associated with adverse effects on mother and foetus.

Lidocaine readily crosses the placenta.

Methylprednisolone acetate with lidocaine
Since adequate human reproductive studies have not been done with methylprednisolone acetate with lidocaine, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Depo-Medrol with Lidocaine contains benzyl alcohol as a preservative. Benzyl alcohol can cross the placenta (see section 4.4).

Breast-feeding
Methylprednisolone

Corticosteroids are distributed in small amounts in breast milk and may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. However, doses of up to 40 mg daily of methylprednisolone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression.

Lidocaine
Lidocaine is excreted in human breast milk.
Methylprednisolone acetate with lidocaine
This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.
Depo-Medrol with Lidocaine contains benzyl alcohol as a preservative (see section 4.4).

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The incidence of predictable undesirable side effects associated with the use of corticosteroids, including hypothalamic-pituitary-adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and duration of treatment (see section 4.4).

MedDRA ***System Organ Class***	**Frequency**	**Undesirable Effects**
Infections and infestations	***Not Known***	Opportunistic infection[e]; Infection[e] (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs), Injection site infection; Peritonitis[c,e]; Recurrence of dormant tuberculosis
Blood and lymphatic system disorders	***Not Known***	Leukocytosis[e]
Immune system disorders	***Not Known***	Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction[e]
Endocrine disorders	***Not Known***	Cushingoid[e] Hypopituitarism [e]; Withdrawal symptoms - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see section 4.4). A 'withdrawal syndrome' [e]; may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

MedDRA ***System Organ Class***	**Frequency**	**Undesirable Effects**
Metabolism and nutrition disorders	***Not Known***	Metabolic acidosis[e], Sodium retention[e]; Fluid retention[e], Alkalosis hypokalaemic[e]; Dyslipidaemia[e], Glucose tolerance impaired[e]; Increased requirements for insulin (or oral hypoglycemic agents in diabetics) [a,e], Lipomatosis[e], Increased appetite (which may result in Weight increased)
Psychiatric disorders	***Not Known***	Affective disorder[e] (including Depressed mood[e], Euphoric mood, Affect lability[e], psychological dependence, Suicidal ideation[e]), Psychotic disorder[e] (including Mania[e], Delusion[e], Hallucination[e], and Schizophrenia[e] [aggravation of]); Confusional state; Mental disorder[e]; Anxiety; Personality change[e]; Mood swings[e]; Abnormal behaviour[e]; Insomnia[e], Irritability[e], Nervousness[d]
Nervous system disorders	***Not Known***	Epidural lipomatosis[e] , Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension] [e]); Loss of consciousness[d]; Seizure; Amnesia[e]; Cognitive disorder[e]; Tremor[d], Somnolence[d], Hypoaesthesia[d], Dizziness; Headache[e];
Eye disorders	***Not Known***	Exophthalmos[e]; Vision blurred[d] (See also section 4.4); chorioretinopathy [e]; Cataract[e]; Glaucoma[e]; Diplopia[d] ; Rare instances of blindness associated with intralesional therapy around the face and head; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease
Ear and labyrinth disorders	***Not Known***	Vertigo[e], Tinnitus[d]
Cardiac disorders	***Not Known***	Cardiac arrest[d] , Cardiac failure congestive (in susceptible patients) [e] , Bradycardia[d]
Vascular disorders	***Not Known***	Circulatory collapse[d]; Hypertension[e]; Hypotension; Embolism arterial, Thrombotic events[e]
Respiratory, thoracic and mediastinal disorders	***Not Known***	Respiratory arrest[d], Respiratory depression[d], Pulmonary embolism[e], Hiccups[e]
Gastrointestinal disorders	***Not Known***	Peptic ulcer[b,e] (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage) Gastric haemorrhage[e]; Intestinal perforation[e]; Pancreatitis[e]; Oesophagitis ulcerative[e]; Oesophagitis; Oesophageal candidiasis; Abdominal pain[e]; Abdominal distension[e]; Diarrhoea[e]; Dyspepsia[e]; Nausea[e], Vomiting[d]
Hepatobiliary disorders	***Not Known***	Hepatitis, Increase of liver enzymes

MedDRA *System Organ Class*	Frequency	Undesirable Effects
Skin and subcutaneous tissue disorders	***Not Known***	Angioedema[e]; Petechiae; Ecchymosis[e]; Skin atrophy[e]; Skin striae[e]; Skin hyperpigmentation[e]; Skin hypopigmentation[e]; Hirsutism[e]; Rash[e]; Erythema[e]; Pruritus[e]; Urticaria; Acne[e]; Hyperhidrosis[e] Skin lesion[d]
Musculoskeletal and connective tissue disorders	***Not Known***	Muscular weakness[e],Osteonecrosis[e]; Osteoporosis[e]; Pathological fracture[e]; Muscle atrophy[e]; Myopathy[e]; Neuropathic arthropathy[e]; Growth retardation[e]; Arthralgia; Myalgia[e]; Muscle twitching[d]
Reproductive system and breast disorders	***Not Known***	Menstruation irregular
General disorders and administration site conditions	***Not Known***	Impaired healing[e]; Oedema peripheral[e]; Injection site reaction[e]; Abscess sterile[e]; Fatigue[e]; Malaise[e]; Feeling cold[d], Feeling hot[d]
Investigations	***Not Known***	Intraocular pressure increased[e], Alanine aminotransferase increased[e]; Aspartate aminotransferase increased; Blood alkaline phosphatase increased[e]; Blood potassium decreased[e] ; Carbohydrate tolerance decreased[e]; Urine calcium increased[e];; Blood urea increased[e]; Nitrogen balance negative (due to protein catabolism); Suppression of reactions to skin tests[a,e]
Injury, poisoning and procedural complications	***Not Known***	Tendon rupture[e] (particularly of the Achilles tendon); Spinal compression fracture[e]. Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury.

[a] Not a MedDRA Preferred term.
[b] Peptic ulcer perforation and Peptic ulcer haemorrhage.
[c] Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).
[d] Reported for lidocaine only.
[e] Reported for methylprednisolone acetate only.

CERTAIN SIDE EFFECTS REPORTED WITH SOME NON RECOMMENDED ROUTES OF ADMINISTRATION:

Intrathecal/Epidural: Usual systemic corticoid adverse reactions, headache, meningismus, meningitis, paraparesis/paraplegia, spinal fluid abnormalities, nausea, vomiting, sweating, arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, Seizure, sensory disturbances.

Extradural: Wound dehiscence, loss of sphincter control.

Intranasal: Permanent/temporary blindness, allergic reactions, rhinitis.

Ophthalmic (Subconjunctival): Redness and itching, abscess, slough at injection site, residue at injection site, increased intra-ocular pressure, decreased vision - blindness, infection.

Miscellaneous: Scalp, tonsillar fauces, sphenopalatine ganglion: blindness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

Methylprednisolone
Following overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. In such event the patient may require to be supported during any further traumatic episode.

Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic.

Methylprednisolone is dialysable.

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. Convulsions, hypotension and respiratory depression and cardiac events should be treated as necessary. Continual optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC Code: H02AB04
Pharmacotherapeutic group: Anaesthetics, ATC Code: N01BB02

Methylprednisolone
Methylprednisolone acetate is a synthetic glucocorticoid with the actions and use of natural corticosteroids. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention. However the slower metabolism of the synthetic corticosteroid with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

Lidocaine
Lidocaine has the actions of a local anaesthetic which reversibly blocks nerve conduction near the site of application or injection.

5.2 Pharmacokinetic properties

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 (tmax) 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 (Cmax) 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 C_{max} 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 foetus is less than in the mother, which results in lower total plasma concentrations in the foetus.

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 section 4.5.)

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.

Elimination:

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-hydroxy-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.

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

5.3 Preclinical safety data

Methylprednisolone

Based on conventional studies of safety pharmacology and repeated dose toxicity, no unexpected hazards were identified. The toxicities seen in the repeated-dose studies were those expected to occur with continued exposure to exogenous adrenocortical steroids.

Mutagenesis:

Methylprednisolone has not been formally evaluated for genotoxicity. Studies using structurally related analogues of methylprednisolone showed no evidence of a potential for genetic and chromosome mutations in limited studies in bacteria and mammalian cells.

Carcinogenesis:

Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. Variable results have been obtained with other glucocorticoids tested for carcinogenicity in mice and rats. However, published data indicate that several related glucocorticoids including budesonide, prednisolone, and triamcinolone acetonide can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats. These tumorigenic effects occurred at doses which were less than the typical clinical doses on a mg/m^2 basis. The clinical relevance of these findings is unknown.

Reproductive toxicity:

Methylprednisolone has not been evaluated in animal fertility studies. Corticosteroids have been shown to reduce fertility when administered to rats. Adverse effects on fertility in male rats administered corticosterone were observed and were reversible. Decreased weights and microscopic changes in prostate and seminal vesicles were observed. The numbers of implantations and live foetuses were reduced and these effects were not present following mating at the end of the recovery period.

An increased frequency of cleft palate was observed among the offspring of mice treated during pregnancy with methylprednisolone in doses similar to those typically used for oral therapy in humans.

An increased frequency of cardiovascular defects and decreased body weight were observed among the offspring of pregnant rats treated with methylprednisolone in a dose that was similar to that used for oral therapy in humans but was toxic to the mothers. In contrast, no teratogenic effect was noted in rats with doses <1-18 times those typically used for oral therapy in humans in another study. High frequencies of foetal death and a variety of central nervous system and skeletal anomalies were reported in the offspring of pregnant rabbits treated with methylprednisolone in doses less than those used in humans. The relevance of these findings to the risk of malformations in human infants born to mothers treated with methylprednisolone in pregnancy is unknown. Safety margins for the reported teratogenic effects are unknown.

Lidocaine

Carcinogenesis:

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

A metabolite of lidocaine, 2,6-xylidine, has been shown to be carcinogenic in rats with unknown clinical relevance in relation to short-term/intermittent use of lidocaine as a local anaesthetic.

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

Methylprednisolone plus Lidocaine

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

The toxicity of lidocaine was not significantly altered in rats that were treated with the combination of lidocaine and methylprednisolone.

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol,
benzyl alcohol (E1519),
Sodium chloride,
myristyl-gamma-picolinium chloride,
sodium hydroxide,
hydrochloric acid
water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials..

6.4 Special precautions for storage

Store below 25ºC.
Do not freeze.

6.5 Nature and contents of container

Glass vials with rubber cap containing 2 ml of suspension.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENCE HOLDER:

Pfizer PFE pharmaceuticals Israel, 9 Shenkar St., Herzliya Pituach 46725.

8. LICENCE NUMBER:

045-97-23829

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