DEPO-MEDROL™ with Lidocaine Injection
(Methylprednisolone acetate, Lidocaine hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

DEPO-MEDROL™ with Lidocaine injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Methylprednisolone acetate 40 mg and Lidocaine hydrochloride 10 mg.

Excipient with known effect:
DEPO-MEDROL with Lidocaine contains 8.7 mg of benzyl alcohol in each 1 ml vial and 17.4 mg of benzyl alcohol in each 2 ml vial, which is equivalent to 8.7 mg/ml of benzyl alcohol.

3. PHARMACEUTICAL FORM

Sterile aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glucocorticoids should be considered as symptomatic treatment only.

FOR INTRASYNOVIAL, PERIARTICULAR OR INTRABURSAL ADMINISTRATION (see section 4.4)

DEPO-MEDROL with Lidocaine is indicated as adjunctive therapy for short-term administration (to assist the patient over an acute episode or exacerbation) in:

- Synovitis in cases of osteoarthritis
- Rheumatoid arthritis
- Acute and subacute bursitis
- Acute gouty arthritis
- Epicondylitis
- Acute non-specific tenosynovitis
- Post-traumatic osteoarthritis

DEPO-MEDROL with Lidocaine infiltration may also be useful in the treatment of cystic tumours, of an aponeurosis or tendinitis (ganglia).

DEPO-MEDROL with Lidocaine is indicated in adults.

4.2 Posology and method of administration

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

1. RHEUMATOID ARTHRITIS 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	Dose range
Large	Knees Ankles Shoulders	20 to 80 mg
Medium	Elbows Wrists	10 to 40 mg
Small	Metacarpophalangeal Interphalangeal Sternoclavicular Acromioclavicular	4 to 10 mg

It is recommended for the anatomy of the joint involved to be reviewed before attempting intra-articular injection. In order to obtain the full anti-inflammatory effect, it is important for the injection to be made into the synovial space. Employing the same sterile technique as for a lumbar puncture, a sterile needle, 20 to 24 gauge, (on a dry syringe) is quickly inserted into the synovial cavity. The aspiration of a few drops of synovial fluid proves that the joint space has been penetrated. The injection site for each joint is determined by that location where the synovial cavity is most superficial and mostly 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 quantity 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 injection site should be covered with a 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 intra-articular injection are those that are anatomically inaccessible such as the spinal joints and those devoid of a synovial space, such as the sacroiliac joints. Treatment failures are most frequently the result of penetration outside the synovial cavity. Little or no benefit follows injection into surrounding tissue. If treatment fails when injection into the synovial space is certain, as determined by aspiration of fluid, repeated injections are usually futile. Local treatment does not alter the underlying disease process, and whenever possible comprehensive treatment including physiotherapy and orthopaedic correction should be employed.

2. BURSITIS

The area around the injection site should be cleaned carefully and an infiltration at the site made with 1% 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 switched 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 to inject the suspension into the tendon sheath rather than into the substance of the tendon. The tendon may be readily palpated when stretched. When treating conditions such as

epicondylitis, the area of greatest tenderness should be outlined carefully and the suspension infiltrated into this region. For ganglia of the tendon sheaths, the suspension is injected directly into the cyst.

According to the severity of the condition, the dose may range from 4 to 30 mg. In recurrent or chronic conditions, repeated injections may be necessary. Normal sterile precautions should be observed for each injection (application of an appropriate antiseptic onto the skin).

Paediatric population
DEPO-MEDROL with Lidocaine has not been studied in the paediatric population.
DEPO-MEDROL with Lidocaine is contraindicated in premature or term newborns (aged 0 to 4 weeks) (see section 4.3).
DEPO-MEDROL with Lidocaine should not be used unless it is absolutely necessary and if no other solution is feasible (see section 4.4).

Method of administration:
- Intrasynovial, periarticular or intrabursal
- Intra- and sublesional

DEPO-MEDROL with Lidocaine should not be administered by any route other than those listed under "4.1 Therapeutic indications" (also see the section "Side effects reported with contraindicated routes of administration" in section 4.4).

4.3 Contraindications

- Hypersensitivity to methylprednisolone acetate, lidocaine hydrochloride, local anaesthetics of amide type or to any of the excipients
- Intrathecal administration
- Intravenous administration
- Epidural administration
- Intranasal and ophthalmic administration and diverse injection sites (scalp, oropharynx, sphenopalatine ganglion)
- Systemic fungal infections
- Administration to premature or term newborns (see sections 4.2 and 4.4 – paediatric population)

4.4 Special warnings and precautions for use

This product contains benzyl alcohol, which is potentially toxic when administered locally to neural tissue (see "Paediatric population" below).

While crystals of adrenal steroids in the dermis suppress inflammatory reactions, their presence may cause disintegration of the cellular elements and physicochemical changes in the basic substance of the connective tissue. The infrequently occurring dermal and/or subdermal changes that result 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 adrenal steroid crystals have been absorbed.

In order to minimise the incidence of dermal and subdermal atrophy, care must be exercised not to exceed the recommended doses. Multiple small injections into the area of the lesion should be made whenever possible. The technique of intra-articular and intramuscular injection should also include precautions against injection or leakage into the dermis. Methylprednisolone acetate with lidocaine should not be administered by any route other than those listed in section 4.1. It is critical to observe all appropriate techniques, and for all

necessary precautions be taken to during administration of methylprednisolone acetate with lidocaine in order to ensure the correct diffusion of the medicinal product.

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

The use of a single vial of DEPO-MEDROL with Lidocaine to administer multiple doses requires special care to avoid contamination (see section 6.4).

There is some evidence that benzalkonium chloride is not an adequate antiseptic for sterilising multidose vials. A povidone-iodine solution or a similar product is recommended to cleanse the vial cap prior to aspiration of the contents (see section 6.4).

Intra-articular use
In case of intra-articular use and/or other local administration, strict sterile technique is required to avoid iatrogenic infections.

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 to detect deterioration is suggested in some cases.

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

The following additional precautions apply for parenteral administration of corticosteroids.
Intrasynovial injection of corticosteroids may produce systemic as well as local effects. No additional benefit derives from the intramuscular administration of methylprednisolone with lidocaine. When parenteral treatment with corticosteroids is desirable for sustained systemic action, methylprednisolone acetate alone should be used.

An adequate examination of any joint fluid present should be carried out in order to exclude septic processes. A marked increase in pain accompanied by local swelling, further restriction of joint movement, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, local injection of corticosteroids should be stopped and appropriate antimicrobial treatment should be started.

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

Sterile technique is necessary to prevent infections or contamination.

Immunosuppressant effects/increased susceptibility to infections
Corticosteroids may increase susceptibility to infections or mask certain signs of infection, exacerbate existing infections, increase the risk of reactivation or exacerbation of latent infections, and new infections may appear during their use. There may be decreased resistance and inability to localise an infection when corticosteroids are used. Infections caused by any pathogenic agent including bacteria, viruses, fungi, protozoa or helminths, 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. The frequency of infectious complications increases with the dose of corticosteroid. Monitor for the development of infection and consider withdrawal of corticosteroids or dosage reduction as needed.

Do not use intrasynovial, intrabursal or intratendinous administration to obtain a local effect in the presence of an acute infection.

Patients treated with immunosuppressive medicinal products are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, may have a more serious or even fatal course in non-immune children or adults treated with corticosteroids.

Administration of live or live-attenuated vaccines is not recommended in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines and biogenetic vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished or even ineffective. In patients receiving non-immunosuppressive doses of corticosteroids the necessary vaccinations can be administered as usual.

The use of DEPO-MEDROL with Lidocaine in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used in conjunction with appropriate antituberculosis regimen. If corticosteroids are indicated in patients with latent tuberculosis or positive 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.

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. One systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses and one review of the literature suggest that longer courses (5–11 days) of low-dose corticosteroids may 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 corticosteroids, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any medicinal product.

Endocrine effects
In patients treated with corticosteroids subjected to unusual stress, an increased dose of rapidly acting corticosteroids may be required before, during and after the stressful situation.

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

Steroid "withdrawal syndrome", seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuation 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 probably 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.

The effect of corticosteroids is enhanced in patients with hypothyroidism.

Metabolism and nutrition
Corticosteroids, including methylprednisolone, may increase blood glucose, worsen pre-existing diabetes, and predispose patients on long-term corticosteroid therapy to diabetes mellitus.

Latent diabetes may also appear, or the doses of insulin/oral antidiabetic agents may need to be increased.

Psychiatric effects
Psychiatric disorders, ranging from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations may appear during treatment with corticosteroids. Existing emotional instability or psychotic tendencies may also be aggravated by corticosteroids.

Potentially severe adverse psychiatric reactions may occur with systemic steroids. The symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal of the treatment, although specific treatment may be necessary in certain cases.

Psychological effects have been reported upon withdrawal of corticosteroids, though their frequency is not known. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.

Nervous system effects
Corticosteroids should be used with caution in patients with seizures.

Corticosteroids should be used with caution in patients with myasthenia gravis (see remarks on myopathy in the section "Musculoskeletal effects" below).

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

Ocular effects
Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves and promote the appearance of secondary fungal or viral infections of the eye.

Corticosteroids should be used with caution in patients with ocular herpes simplex or herpes zoster associated with ocular symptoms due to the risk of corneal perforation.

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.

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

Cardiac effects
Side effects of glucocorticoids on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose treated patients with other existing cardiovascular risk factors to additional cardiovascular effects, in case of prolonged high-dose treatment. Accordingly, corticosteroids should be used with caution in such patients. Attention should be paid to changes in risk, and additional cardiac monitoring should be provided if required.

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

Vascular effects
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.

Corticosteroids should be used with caution in patients with hypertension.

Gastrointestinal effects
High doses of corticosteroids may produce acute pancreatitis.

There is no universal consensus regarding the involvement of corticosteroids *per se* in the appearance of peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer and 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 non-specific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infections. 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, an appropriate monitoring is required.

Musculoskeletal effects
An acute myopathy has been reported with 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 generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Increased creatine kinase levels may also occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Osteoporosis is a common but rarely recognised adverse effect associated with a long-term use of high doses of glucocorticoids.

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.

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

Investigations
Average and high 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 synthetic derivatives except when used at high doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Treatment with corticosteroids must be taken into consideration when interpreting certain biological tests and parameters (e.g., skin tests, thyroid hormone levels).

Other
Since complications of treatment with glucocorticoids are dependent on the dose and the duration of treatment, the dose, frequency and duration administration (daily or alternate-day), a decision must be made in each individual case, taking into consideration the risks and benefits.

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).

Acetylsalicylic acid and nonsteroidal anti-inflammatory agents should be used with caution in combination with corticosteroids.

Concomitant use of oral anticoagulants and methylprednisolone may increase the risk of bleeding. There are reports of diminished effects of oral anticoagulants as well. For patients treated with vitamin K antagonists, more frequent monitoring of prothrombin time (INR) is recommended, especially during treatment initiation or dose adjustments of methylprednisolone (see section 4.5).

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.

Excipients information
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium-free’.

Paediatric population
DEPO-MEDROL with Lidocaine contains benzyl alcohol (see section 2).

Benzyl alcohol may cause allergic reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol must not be given to a newborn baby (up to 4 weeks old), unless recommended by the doctor. Due to increased risk due to accumulation in young children, benzyl alcohol must not be used for more than a week in young children (less than 3 years old), unless advised by the doctor or pharmacist (see sections 4.2 – paediatric population and 4.3). High volumes should be used with caution and only if necessary, especially in pregnant or breast-feeding women or in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily divided dose glucocorticoid therapy. The use of such a regimen should therefore be restricted to those most serious indications.

Infants and children treated with corticosteroids in the long term are at particular risk of increased intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

4.5 Interaction with other medicinal products and other forms of interaction

Methylprednisolone is a cytochrome P450 (CYP) substrate and is mainly metabolised by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyses 6β-hydroxylation of steroids, the essential Phase 1 metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (along with other medicinal products) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS such as ketoconazole, itraconazole, clarithromycin and grapefruit juice, generally decrease hepatic clearance and increase the plasma concentration of methylprednisolone. In the presence of a CYP3A4 inhibitor, methylprednisolone dose reduction may be required to avoid steroid linked toxicity.

CYP3A4 INDUCERS such as rifampin, carbamazepine, phenobarbital and phenytoin generally increase hepatic clearance, and decrease plasma concentrations of methylprednisolone. In the presence of a CYP3A4 inducer the dose of methylprednisolone may need to be increased to achieve the desired effect.

In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected necessitating an appropriate adjustment of the dose. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with co-administration.

Methylprednisolone also interacts with certain other medicinal products unrelated to CYP3A4 metabolism.

Table 1 provides a list and description of the drug interactions and the most frequent and/or clinically significant effects observed with methylprednisolone.

Table 1. Important drug or substance interactions/effects with methylprednisolone

Class or type of medicinal product - MEDICINAL PRODUCT or SUBSTANCE	**Interaction/effect**
Antibiotics, anti-tuberculosis treatments - RIFAMPIN	CYP3A4 INDUCTOR
Oral anticoagulants (Vitamin K antagonists and non-vitamin K antagonists)	The effect of the concomitant use of methylprednisolone with oral anticoagulants could vary. Reports mention both decreases and increases in the effects of these anticoagulants in cases of concomitant administration with corticosteroids. Coagulation indices should therefore be monitored in order to maintain the desired anticoagulant effects.

Class or type of medicinal product **- MEDICINAL PRODUCT or SUBSTANCE**	**Interaction/effect**
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCTOR (and SUBSTRATE)
Anticonvulsants - PHENOBARBITAL - PHENYTOIN	CYP3A4 INDUCERS
Anticholinergics - NEUROMUSCULAR BLOCKING AGENTS	Corticosteroids can influence the action of anticholinergics. 1) Acute myopathy has been reported during concomitant administration of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking agents (see section 4.4, "Musculoskeletal effects," for more information). 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may occur with all competitive neuromuscular blocking agents.
Antidiabetics - INSULIN ORAL ANTIDIABETICS	Glucocorticoids may increase the need for oral insulin or hypoglycaemic agents in diabetic patients.
Antiemetics - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungals - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce metabolism of HIV protease inhibitors, resulting in decreased plasma concentrations.
Pharmacokinetic enhancers - COBICISTAT	CYP3A4 INHIBITORS
Calcium antagonists - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE)
Oral contraceptives: - ETHINYLESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE)
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR
+ Immunosuppressants - CICLOSPORIN	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Concomitant use of ciclosporin and methylprednisolone results in mutual inhibition of their metabolism, which may increase plasma concentrations of one or both substances. It is therefore possible that the undesirable effects associated with the use of each medicinal product when used as monotherapy may have a higher incidence when used in combination.

Class or type of medicinal product **- MEDICINAL PRODUCT or SUBSTANCE**	**Interaction/effect**
	2) Convulsions have been reported with concomitant use of methylprednisolone and ciclosporin.
+ Immunosuppressants - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES
Macrolide antibiotics - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide antibiotics - TROLEANDOMYCIN	CYP3A4 INHIBITOR
NSAIDs (non-steroidal anti-inflammatory drugs) - High dose acetylsalicylic acid	1) In the event of concomitant administration of corticosteroids and NSAIDs, the incidence of haemorrhage and gastrointestinal ulceration may be increased. 2) Methylprednisolone may increase the clearance of high-dose acetylsalicylic acid. This decrease in serum salicylates may result in an increased risk of salicylate toxicity when methylprednisolone is discontinued.
Potassium wasting agents - DIURETICS THIAZIDE DIURETICS	The combination of glucocorticoids and thiazide diuretics increases the risk of glucose intolerance, and increases the risk of hypokalaemia.
Vaccines	The administration of live-attenuated vaccines is not recommended in patients receiving immunosuppressive doses of corticosteroids. Inactivated vaccines and biogenetic vaccines can be administered to these patients, but the therapeutic response to these vaccines may be diminished or even be ineffective. In patients receiving non-immunosuppressive doses of corticosteroids, the necessary vaccinations can be administered as usual.
Desired interaction - Tuberculosis	In the treatment of fulminating or disseminated pulmonary tuberculosis and in the treatment of either suspected or existing tuberculous meningitis with subarachnoid block, methylprednisolone should be administered in combination with suitable tuberculostatics.
Desired interaction - neoplastic disorders	In the treatment of neoplastic diseases such as leukaemia and lymphoma, methylprednisolone is typically used in combination with alkylating agents, antimetabolites and vinca alkaloids.

4.6 Fertility, pregnancy and lactation

Pregnancy

Methylprednisolone
Some animal studies have shown that corticosteroids, including methylprednisolone, when administered during gestation, in high doses, may cause foetal development malformation,

including cleft palates, intrauterine growth retardation and effects on growth and brain's development (see section 5.3). There are no data indicating that corticosteroids result in a higher incidence of congenital malformations such as cleft palate/harelip in humans. Corticosteroids readily cross the placenta.

One retrospective study found an increased incidence of low birth weights in children 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 for the shortest duration possible.

Neonates born of mothers, who have received substantial doses of glucocorticoids during pregnancy, must be closely monitored for signs of adrenal insufficiency, although neonatal adrenal insufficiency appears to be rare in neonates who were exposed *in utero* to corticosteroids.

Lidocaine
Lidocaine readily crosses the placenta.

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

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 foetus.

There are no known effects of corticosteroids on labour and delivery.

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

Benzyl alcohol can cross the placenta (see section 4.4).

Breast-feeding

Methylprednisolone
Corticosteroids are excreted in breast milk.

Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants.

Lidocaine
Lidocaine is excreted in 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.

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

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive or use machines has not been systematically evaluated.

Undesirable effects, such as dizziness, vertigo, visual disturbances and fatigue are possible after treatment with corticosteroids. If they experience one of these effects, patients should not drive or use machines.

4.8 Undesirable effects

Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurological events have been reported with and without use of fluoroscopy. The safety and effectiveness of epidural administration of corticosteroids have not been established, and corticosteroids are not approved for this use.

The following undesirable effects have been observed and reported during treatment with DEPO-MEDROL with Lidocaine at the following frequencies:

Common (≥1/100 and <1/10)
Frequency not known (cannot be estimated from the available data)

The following undesirable effects have been reported with the following contraindicated routes of administration:

Intrathecal route/epidural route: arachnoiditis, functional gastrointestinal disorders, bladder disorders, headache, meningitis, paraparesis/paraplegia, seizures, sensory disorders.
The frequency of these undesirable effects is not known.

Intranasal route: temporary or permanent visual disorders going as far as blindness; allergic reactions; rhinitis.

Ophthalmic route: temporary or permanent visual disorders going as far as blindness, increased intra-ocular pressure, ocular and peri-ocular inflammation and allergic reactions, infections, residue or atrophy at the injection site.

Miscellaneous injection sites: (scalp, oropharynx, sphenopalatine ganglion): blindness.

System organ class	Frequency	Undesirable effects
Infections and infestations	Frequency not known	Infections***, opportunistic infection***, masked infections***, activation of latent infections***, peritonitis[#]/***
Blood and lymphatic system disorders	Frequency not known	Leukocytosis***
Immune system disorders	Frequency not known	Hypersensitivity***, anaphylactic reaction, anaphylactoid reaction***
Endocrine disorders	Frequency not known	Cushingoid syndrome***, hypothalamic pituitary adrenal axis suppression***, steroid withdrawal syndrome***
Metabolism and nutrition disorders	Common	Reactivation of latent diabetes***
	Frequency not known	Metabolic acidosis***, sodium retention***, fluid retention***, hypokalaemic alkalosis***, dyslipidaemia***, impaired glucose tolerance***, increased requirements for insulin (or oral hypoglycaemic agents in

System organ class	Frequency	Undesirable effects
		diabetics)***, lipomatosis***, increased appetite (which may result in weight gain)***
Psychiatric disorders	Frequency not known	Affective disorders*** (euphoric mood, depressed mood***, affect lability***, drug dependence***, suicidal ideation***), psychotic disorders*** (such as mania***, delirium***, hallucinations*** and aggravation of schizophrenia***), confusional state, mental disorders***, anxiety, mood swings***, abnormal behaviour***, personality change***, insomnia***, irritability***, nervousness**
Nervous system disorders	Frequency not known	Increased intracranial pressure (with papilloedema [benign intracranial hypertension])***, convulsive crises, amnesia***, cognitive disorders***, dizziness, headache***, epidural lipomatosis***, loss of consciousness**, tremor**, nervous tics**, rigidity**, hypoaesthesia**, somnolence**
Eye disorders	Frequency not known	Cataract***, glaucoma***, exophthalmos***, rare cases of blindness associated with intralesional treatment of face and head, central serous chorioretinopathy***, diplopia**, vision blurred** (see also section 4.4)
Ear and labyrinth disorders	Frequency not known	Vertigo***, tinnitus**
Cardiac disorders	Frequency not known	Congestive cardiac failure (in susceptible patients)***, myocardial rupture following a myocardial infarction***, bradycardia**, cardiac arrest**
Vascular disorders	Frequency not known	Thrombosis***, hypertension***, hypotension, circulatory collapse**, flushing***
Respiratory, thoracic and mediastinal disorders	Frequency not known	Pulmonary embolism***, hiccups***, persistent hiccups with high corticosteroid doses***, respiratory arrest**, respiratory depression**
Gastrointestinal disorders	Frequency not known	Peptic ulcer*/***, gastric haemorrhage***, intestinal perforation***, pancreatitis***, ulcerative oesophagitis***, oesophagitis***, abdominal pain***, abdominal distension***, diarrhoea, dyspepsia***, nausea***, vomiting**
Skin and subcutaneous tissue disorders	Frequency not known	Angioedema***, petechiae***, ecchymosis***, skin atrophy***, striae***, hyperpigmentation of the skin***, hypopigmentation of the skin***, hirsutism***, rash***,

System organ class	Frequency	Undesirable effects
		erythema***, pruritus***, urticaria, acne***, hyperhidrosis***, skin lesion**
Musculoskeletal and connective tissue disorders	Frequency not known	Muscle weakness***, osteonecrosis***, pathological fracture***, muscle atrophy***, osteoporosis***, myopathy***, neuropathic arthropathy***, arthralgia***, growth retardation***, myalgia***, muscle contractions**, post injection pain flare (following intra-articular, periarticular, and tendon sheath injections)[a/]***
Reproductive system and breast disorders	Frequency not known	Irregular menstruation***
General disorders and administration site conditions	Frequency not known	Impaired healing***, injection site reactions***, feeling cold**, feeling warm**, fatigue***, malaise***, sterile abscess***, oedema**, peripheral oedema***, injection site infections following non-sterile administration. With *in situ* administration: dermal and subdermal atrophy, depressions in the skin at the injection site***
Investigations	Frequency not known	Increased alanine aminotransferase***, increased aspartate aminotransferase***, increased blood alkaline phosphatase***, increased intraocular pressure***, decreased carbohydrate tolerance***, decreased blood potassium***, increased urine calcium***, suppression of reactions to skin tests***, increased blood urea***
Injury, poisoning and procedural complications	Frequency not known	Tendon rupture (particularly of the Achilles tendon)***, spinal compression fracture***

* Perforation due to peptic ulcer, haemorrhage due to peptic ulcer
** Undesirable effect reported only with lidocaine
*** Undesirable effect reported only with methylprednisolone acetate
[#] peritonitis may be the first sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4)
[a] not a MedDRA Preferred Term

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.

4.9 Overdose

Methylprednisolone:
Reports of acute toxicity and/or death following overdose with corticosteroids are rare.

Repeated frequent doses (daily or several times per week) over a protracted period may result in typical complications such as a Cushing syndrome.

In the event of overdose, no specific antidote is available; supportive and symptomatic treatment should be initiated.

Methylprednisolone is dialysable.

Lidocaine:
Overdose with lidocaine can manifest as a transient stimulation of the central nervous system, of which the early symptoms are: yawning, restlessness, dizziness, nausea, vomiting, dysarthria, ataxia, auditive and visual disturbances. Moderate intoxication can also cause twitching and convulsions. This can be followed by unconsciousness, respiratory depression and coma. Very severe intoxication, associated with decreased myocardial contractility and delayed impulse conduction, hypotension and cardiovascular collapse can be expected to be followed by a complete heart block and cardiac arrest. Treatment is symptomatic, and where appropriate, convulsions may be treated with diazepam. Ventilation may be necessary in case of respiratory depression. Hypotension may be treated by the administration of fluids and dopamine. Similarly, in case of asystole, epinephrine may be administered and, if necessary, a pacemaker may be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group of methylprednisolone acetate: glucocorticoids. ATC code: H02AB04

DEPO-MEDROL with Lidocaine is a sterile aqueous suspension of the synthetic glucocorticoid methylprednisolone acetate and lidocaine hydrochloride, a local anaesthetic. Methylprednisolone acetate is a strong anti-inflammatory glucocorticoid with a prolonged action. It inhibits local inflammations caused by mechanical, chemical or immunological factors. Lidocaine is a potent local anaesthetic of the amide type.

Methylprednisolone:
Methylprednisolone acetate has the general properties of methylprednisolone but is less soluble and less readily metabolised, which explains its prolonged activity. It has a greater potency than prednisolone and induces less sodium and water retention, potassium loss and hypertension. Like methylprednisolone, the advantages of methylprednisolone acetate over older generation corticoids lies in its ability to achieve equivalent anti-inflammatory effects at a lower dose. A dose of 4.4 mg methylprednisolone acetate is considered to be equivalent to 20 mg hydrocortisone.

Glucocorticoids diffuse across cell membranes and form complexes with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin) and stimulate transcription of mRNA and synthesis of various enzymes thought to be ultimately responsible for the numerous effects of systemic use of glucocorticoids.

The maximum pharmacological activity of corticosteroids lags peak blood concentrations, suggesting that most of the effects of these substances result from modifications of enzyme activity rather than direct actions.

Lidocaine:
Lidocaine hydrochloride produces insensitivity and loss of pain without loss of motor nervous control by preventing or diminishing the conduction of nerve impulses along nerve fibres and at nerve endings. When injected lidocaine hydrochloride has a rapid onset of action and its effects are reversible, more intense and more prolonged than those of procaine.

5.2 Pharmacokinetic properties

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

Absorption

Methylprednisolone:
Methylprednisolone acetate is hydrolysed to its active form by serum cholinesterases.

One in-house study of eight volunteers determined the pharmacokinetics of a single 40 mg intramuscular dose of methylprednisolone acetate. The average of the individual peak plasma concentrations was 14.8 ± 8.6 ng/ml, the average of the individual peak times (T_{max}) was 7.25 ± 1.04 hours, and the average area under the curve (AUC) was 1354.2 ± 424.1 ng/ml x h (Day 1-21).

An intra-articular injection of 40 mg in both knees (total dose: 80 mg) gives after 4 to 8 hours serum methylprednisolone peaks of approximately 21.5 µg/100 ml.

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

Lidocaine:
Lidocaine hydrochloride is rapidly absorbed from injection sites and rapidly spreads through surrounding tissues.

The pharmacokinetics of lidocaine were studied with different maximum concentration (C_{max}) values reported after synovial absorption, following an intra-articular bolus injection in patients undergoing knee joint arthroscopy. The C_{max} values were 2.18 µg/ml at 1 hour (serum) and 0.63 µg/ml at 0.5 hours (plasma), following administration of lidocaine doses of 7 mg/kg and 400 mg, respectively. Other reported serum C_{max} values were 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 of 20 ml of 1.5%, respectively.

There are no available pharmacokinetic data concerning lidocaine after intra-bursa and intra-cyst administrations for local effect.

Distribution

Methylprednisolone:
Methylprednisolone is widely distributed in 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%.

In humans, methylprednisolone forms a weak dissociable bond with albumin and transcortin.

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 α_1-acid glycoprotein.

Lidocaine has a volume of distribution at the 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.

Lidocaine crosses into the cerebrospinal fluid.

Biotransformation

Methylprednisolone:
In humans, methylprednisolone is metabolised in the liver to inactive metabolites, principally 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver is primarily via CYP3A4. The list of drug interactions based on CYP3A4-mediated metabolism is found in section 4.5.

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for p-glycoprotein, a protein in the ATP-binding cassette (ABC) transport protein family, which influences tissue distribution and interactions with other medicinal products modulated by P-gp.

Lidocaine:
Lidocaine is mainly metabolised by the liver. The principal metabolites of lidocaine are monoethylglycine xylidide, glycinexylidide, 2,6-dimethylaniline, and 4-hydroxy-2,6-dimethylaniline. 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.

The metabolites are excreted in the urine as glucuronides, sulfates and unconjugated compounds. These conjugation reactions occur principally in the liver, but also to some extent in the kidneys.

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 Populations

Methylprednisolone:

Sex

The clearance of methylprednisolone was higher in healthy women than in healthy men after intravenous administration of a single dose: 0.45 versus 0.29 l/h/kg. There were nonetheless no differences in pharmacodynamic measures.

Elderly patients
Methylprednisolone clearance in healthy elderly men (69–82 years) was lower than in younger men (24–37 years) after intravenous administration of a single dose: 0.24 *versus* 0.36 l/h/kg.

Paediatric population
The clearance of methylprednisolone is mildly related to age. Younger subjects tend to metabolise methylprednisolone more rapidly. In one study of intravenous administration of a single dose in 14 patients with nephrotic syndrome, younger subjects (<13 years) showed greater clearance than the older group (>13 years): 0.53 *versus* 0.38 l/h/kg.

Renal impairment
In a single-dose intravenous study in 6 male subjects with chronic renal impairment, the pharmacokinetics of methylprednisolone remained unchanged compared to healthy controls, with an average clearance of 0.28 l/h/kg. In addition, no differences in pharmacodynamic measures were observed in these subjects with chronic renal failure.

Hepatic impairment
In a single-dose intravenous study in 6 male subjects with chronic liver disease, the pharmacokinetics of methylprednisolone were similar to those in healthy controls, with an average clearance of 0.29 l/h/kg.

Lidocaine:

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

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

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

No pharmacokinetic data are available concerning lidocaine after intra-articular, intra-bursal and intra-cyst administrations for local effect in patients with renal impairment.

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 are those expected to occur with continued exposure to exogenous glucocorticoids.

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.

Mutagenesis
Methylprednisolone has not been formally evaluated for genotoxicity. However, there is no evidence of mutagenesis in structurally similar glucocorticoids.

Reproductive toxicity
Corticosteroids have been shown to reduce fertility when administered to rats at low multiples of the human dose based on a mg/m^2 basis.

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. In animal reproduction studies, glucocorticoids such as methylprednisolone have been shown to increase the incidence of malformations (cleft palate, skeletal malformations), embryo-foetal lethality (e.g., increase in resorptions) and intra-uterine growth retardation.

Lidocaine

Carcinogenesis
No long-term studies in animals have 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
No adverse effects were demonstrated in a multi-generational reproductive toxicity study.

Methylprednisolone plus lidocaine

Based on conventional studies of repeated-dose toxicity and intra-articular toxicity, no unexpected hazards were identified. The toxicities seen in the repeated-dose studies are those expected to occur with continued exposure to exogenous glucocorticoids.

Carcinogenesis
Carcinogenicity studies have not been conducted with the combination of methylprednisolone and lidocaine (see above the carcinogenicity for each individual drug separately).

Mutagenesis
Genotoxicity studies have not been conducted with the combination of methylprednisolone and lidocaine (see above the genotoxicity for each individual drug separately).

Reproductive toxicity

Reproductive toxicity studies have not been conducted with the combination of methylprednisolone and lidocaine (see above the reproductive toxicity for each individual drug separately).

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.2 Shelf-life

Please refer to outer carton for expiry date.

6.3 Special precautions for storage

Please refer to outer carton for storage condition.

6.4 Special precautions for disposal and other handling

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Shake before using.

MULTIDOSE USE OF VIALS
Multidose use of a vial of DEPO-MEDROL with Lidocaine requires special care to avoid contamination. Although the content of these vials is initially sterile, any multidose use of vials may lead nevertheless to contamination unless strict aseptic technique is observed. Particular care, such as the use of disposable sterile syringes and needles, should be observed if intrasynovial use is intended. There is some evidence that benzalkonium chloride is not an adequate antiseptic for sterilizing DEPO-MEDROL with Lidocaine multidose vials. A povidone-iodine solution or a similar product is recommended to cleanse the vial top prior to aspiration of contents.

Multidose use of DEPO-MEDROL with Lidocaine vials is not recommended for intrasynovial injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Pfizer Corporation Hong Kong Limited
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