# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Depo-Medrone 40mg/ml with Lidocaine 10mg/ml Suspension for Injection, 2ml vial

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains methylprednisolone acetate 40 mg and lidocaine hydrochloride monohydrate10 mg.
Each vial contains 80 mg methylprednisolone acetate and 20 mg lidocaine hydrochloride monohydrate.

Excipient 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.
Sterile white aqueous suspension.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Depo-Medrone with Lidocaine is indicated in conditions requiring a glucocorticoid effect: e.g. anti-inflammatory or anti-rheumatic. It is recommended for local use where the added anaesthetic effect would be considered advantageous.

### 4.2 Posology and method of administration

Depo-Medrone with Lidocaine should not be mixed with any other preparation as flocculation of the product may occur. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever suspension and container permit.

Therapy with Depo-Medrone 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.

Depo-Medrone with Lidocaine may be used by any of the following routes: intra-articular, periarticular, intrabursal, and into the tendon sheath. It **must not** be used by the intrathecal or intravenous routes (see sections 4.3 and 4.8).

Undesirable effects may be minimised by using the lowest effective dose for the minimum period (see section 4.4).

Depo-Medrone with Lidocaine vials are intended for single dose use only.

*Intra-articular:* Rheumatoid arthritis, osteo-arthritis. The dose of Depo-Medrone with Lidocaine depends on the size of the joint and the severity of the condition. Repeated injections, if needed, may be given at intervals of one to five or more weeks depending upon the degree of relief obtained from the initial injection.

A suggested dosage guide is: large joint (knee, ankle, shoulder), 20 – 80 mg (0.5 – 2 ml); medium joint (elbow, wrist), 10 – 40 mg (0.25 – 1 ml); small joint (metacarpophalangeal, interphalangeal, sternoclavicular, acromioclavicular), 4 – 10 mg (0.1 – 0.25 ml).

*Periarticular:* Epicondylitis. Infiltrate 4 – 30 mg (0.1 – 0.75 ml) into the affected area.

*Intrabursal:* Subacromial bursitis, prepatellar bursitis, olecranon bursitis. For administration directly into bursae, 4 – 30 mg (0.1 – 0.75 ml). In most acute cases, repeat injections are not needed.

*Into the tendon sheath:* Tendinitis, tenosynovitis, epicondylitis. For administration directly into the tendon sheath, 4 – 30 mg (0.1 – 0.75 ml). In recurrent or chronic conditions, repeat injections may be necessary. In many cases, a single injection causes a marked decrease in the size of the cystic tumour and may effect a disappearance.

Intra-articular injections should be made using precise, anatomical localisation into the synovial space of the joint involved. 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. Suitable sites for intra-articular injection are the knee, ankle, wrist, elbow, shoulder, phalangeal and hip joints. The spinal joints, unstable joints and those devoid of synovial space are not suitable. Treatment failures are most frequently the result of failure to enter the joint space, however, treatment failure may also occur despite a proper injection into the synovial space as confirmed by aspiration of fluid. Intra-articular injections should be made with care as follows: ensure correct positioning of the needle into the synovial space and aspirate a few drops of joint fluid. The aspirating syringe should then be replaced by another containing Depo-Medrone with Lidocaine. To ensure position of the needle synovial fluid should be aspirated and the injection made.

After injection, the joint is moved slightly to aid mixing of the synovial fluid and the suspension. Subsequent to therapy care should be taken for the patient not to overuse the joint in which 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.

Intrabursal injections should be made as follows: the area around the injection site is prepared in a sterile way and local anaesthesia is administered as necessary. A 20-24 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.

In the treatment of tenosynovitis and tendinitis, care should be taken to inject Depo-Medrone with Lidocaine into the tendon sheath rather than into the substance of the tendon. Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with Depo-Medrone with Lidocaine.

The usual sterile precautions should be observed with each injection.

Paediatric population
Dosage should be reduced for infants and children, but should be governed more by the severity of the condition and response of the patient, than by age or size (see section 4.4).

Elderly
When used according to instructions, there is no information to suggest that a change in dosage is warranted in the elderly. Treatment of elderly patients, however, particularly if long term, should be planned bearing in mind the more serious consequences of the common side-effects of corticosteroids in old age and close clinical supervision is required (see section 4.4).

**4.3 Contraindications**

Depo-Medrone with Lidocaine is contraindicated:

- in patients with known hypersensitivity to the active substances, other local anaesthetics of the amide type, or to any of the excipients listed in section 6.1
- in patients who have systemic fungal 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 epidural route of administration (see section 4.8)
- for use by the intravascular (e.g.intravenous) route of administration)
- for use by the intramuscular route of administration
- in patients who exhibit heart block.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see section 4.4).

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

Depo-Medrone with Lidocaine should not be administered by any route other than those listed. It is critical that, during administration of Depo-Medrone with Lidocaine, appropriate technique be used and care taken to assure proper placement of drug.
Severe medical events have been reported in association with the intrathecal / epidural routes of administration (see sections 4.3 and 4.8). Appropriate measures must be taken to avoid intravascular or intramuscular injection (see section 4.9).

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

Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute rebound exacerbation of disease, acute adrenal insufficiency or polyarteritis being tapered off over weeks or months according to the dose and duration of treatment.

During prolonged therapy any intercurrent illness, trauma, anaesthesia or surgical procedure will require a temporary increase in dosage. In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. If corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

**Special Precautions Regarding Use of Lidocaine for Local Anaesthesia**
Facilities for resuscitation should be available when administering local anaesthetics, such as the lidocaine contained in the methylprednisolone with lidocaine solution for injection. Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used and are usually the result of raised plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Systemic toxicity mainly involves the central nervous system and/or the cardiovascular system (see sections 4.8 and 4.9).

As with other local anaesthetics, lidocaine should be used with caution in patients with epilepsy, myasthenia gravis, cardiac conduction disturbances, congestive heart failure, hypovolemia, and bradycardia. Paediatric and elderly or debilitated patients require smaller doses, commensurate with age and physical status.

*The following precautions apply for parenteral corticosteroids:*
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.

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.

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

Intra-synovial injection of a corticosteroid may produce systemic, as well as local effects. Where parenteral corticosteroid therapy for sustained systemic effect is desired, plain methylprednisolone acetate should be used.

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

Corticosteroids should not be injected into unstable joints.

Sterile technique is necessary to prevent infections or contamination.

Since complications of treatment with glucocorticoids are dependent on the amount of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment.

Benzyl alcohol is also potentially toxic when administered locally to neural tissue (see also section 4.4, Excipient information).

**Immunosuppressant Effects/Increased Susceptibility to Infections**
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Do not use intra-synovial, intrabursal or intratendinous administration for local effect in the presence of acute infection.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. 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.

Measles can have a more serious or even fatal course in immunosuppressed patients. In such children or adults, particular care should be taken to avoid exposure to measles. If exposed, prophylaxis with intramuscular pooled immunoglobulin (IVIG) may be indicated. Exposed patients should be advised to seek medical advice without delay.

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished (see section 4.3).

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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

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.

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**
Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

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 also 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**
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.

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

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.

**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 (see section 4.8). 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 (see section 4.5).

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**
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. Therefore, appropriate monitoring is required.

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**
Corticosteroids should be used with caution in patients with renal insufficiency (see section 5.2).

**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.

**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.

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.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

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.

Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone.

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).

Paediatric population (see section 4.2)
Premature and low-birth weight infants may be more likely to develop toxicity.

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 most serious indications and 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-Medrone 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-Medrone 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**

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

CYP3A4 INHIBITORS – Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity.

CYP3A4 INDUCERS – Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Coadministration may require an increase in methylprednisolone dosage to achieve the desired result.

CYP3A4 SUBSTRATES – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with co-administration.

1. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin (CYP3A4 inhibitor and substrate). Since concurrent administration of these agents results in a mutual inhibition of metabolism, 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 (see section 4.4).
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 and ritonavir (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 (e.g. 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.

15. Pharmacokinetic enhancers (cobicistat) - CYP3A4 inhibitors, which are used to treat HIV infections.

**Lidocaine**
Drugs which inhibit the metabolism of lidocaine (e.g., cimetidine) may cause potentially toxic plasma concentrations when lidocaine is given repeatedly in high doses over long periods of time. Such interactions have no clinical relevance during short-term treatment with lidocaine in recommended doses. Lidocaine should be used with caution in patients receiving other local anaesthetics or class Ib antiarrhythmic drugs, as the toxic effects are additive.

**4.6 Fertility, pregnancy and lactation**

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

Pregnancy
*Methylprednisolone*
Corticosteroids cross the placenta. Animal studies have shown reproductive toxicity (see section 5.3). Although observational studies in humans do not support an association between systemic corticosteroids use during pregnancy and the risk of congenital malformations or oral cleft, a risk cannot be excluded due to the limited amount of data from the use of systemic corticosteroids in pregnant women. Since adequate human reproductive studies have not been done with methylprednisolone acetate, this medicinal product should be used during pregnancy only after a careful benefit-risk assessment for the mother and foetus.

Published studies 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.

Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.
Neonates of mothers who received corticosteroid therapy during pregnancy should be observed for signs of hypo-adrenalism and appropriate measures instituted if such signs exist, although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids. Patients with pre-eclampsia or fluid retention require close monitoring.
There are no known effects of corticosteroids on labour and delivery.

*Lidocaine*
Lidocaine readily crosses the placenta.
The use of local anaesthetics such as lidocaine during labour and delivery may be associated with adverse effects on 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 fetus.

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

Breast-feeding
*Methylprednisolone*
Methylprednisolone is excreted in breast milk and infants of mothers taking pharmacological doses of steroids should be monitored carefully for signs of adrenal suppression.

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

*Lidocaine*
It is not known whether 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-Medrone 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, and temporary impairment of mobility and coordination of movement may occur due to the local anaesthetic effect of lidocaine. When outpatient anaesthesia affects areas of the body involved in driving or operating machinery, patients should be advised to avoid these activities until normal function is fully restored.

**4.8 Undesirable effects**

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

In common with other local anesthetics, adverse reactions to lidocaine are rare and are usually the result of raised plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Systemic toxicity mainly involves the central nervous system and/or the cardiovascular system. Neurological signs of systemic toxicity include dizziness or light-headedness, nervousness, tremor, circumoral paraesthesia, tongue numbness, drowsiness, convulsions, coma. Cardiovascular reactions are depressant and may manifest as hypotension, bradycardia, myocardial depression, cardiac arrhythmias, and possibly cardiac arrest or circulatory collapse. Blurred vision, diplopia, and transient amaurosis may be signs of lidocaine toxicity.

| ***MedDRA System Organ Class*** | **Frequency** | **Adverse Drug Reactions** |
|---|---|---|
| ***Infections and infestations*** | ***Not Known*** | Opportunistic infection[e]; Infection[e]; Injection site infection; Peritonitis[c,e]; Recurrence of dormant tuberculosis |
| ***Immune system disorders*** | ***Not Known*** | Drug hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction |
| ***Neoplasms benign, malignant and unspecified (including cysts and polyps)*** | ***Not Known*** | Kaposi's sarcoma; |

| | | |
|---|---|---|
| | | Phaeochromocytoma crisis |
| ***Blood and lymphatic system disorders*** | ***Not Known*** | Leukocytosis |
| ***Endocrine disorders*** | ***Not Known*** | Cushingoid[e]; Hypopituitarism[e]; Steroid 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).<br>A 'withdrawal syndrome' may also occur including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight. |
| ***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 appetite (which may result in weight increased) [e]; Increased requirements for insulin (or oral hypoglycemic agents in diabetics)[a,e]; Lipomatosis |
| ***Psychiatric disorders*** | ***Not Known*** | Affective disorder[e] (including Depressed mood[e], Euphoric mood, Affect lability[e], Drug dependence[e], Suicidal ideation[e]); Psychotic disorder[e] (including Mania[e], Delusion, Hallucination, and Schizophrenia [aggravation of]); Confusional state; Mental disorder; |

| | | |
|---|---|---|
| | | Anxiety; Personality change[e]; Mood swings[e]; Abnormal behaviour[e]; Insomnia[e]; Irritability[e]; Nervousness[d] |
| ***Nervous system disorders*** | ***Not Known*** | Intracranial pressure increased (with Papilloedema [benign intracranial hypertension]) [e]; Seizure; Amnesia[e]; Cognitive disorder[e]; Dizziness; Headache[e]; Epidural lipomatosis |
| ***Eye disorders*** | ***Not Known*** | Exophthalmos[e]; Chorioretinopathy[e]; Cataract[e]; Glaucoma[e]; rare instances of blindness associated with intralesional therapy around the face and head[a]; Increased intra-ocular pressure, with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease; Diplopia[d]; Vision blurred[d] (see section 4.4) |
| ***Ear and labyrinth disorders*** | ***Not Known*** | Vertigo[e]; Tinnitus[d] |
| ***Cardiac disorders*** | ***Not Known*** | Cardiac arrest[d]; Cardiac arrhythmias[d]; Cardiac failure congestive (in susceptible patients)[e]; Bradycardia[d] |
| ***Vascular disorders*** | ***Not Known*** | Circulatory collapse[d]; Thrombosis[e]; Hypertension[e]; Hypotension; Thrombotic events |
| ***Respiratory, thoracic and mediastinal disorders*** | ***Not Known*** | Respiratory arrest[d]; Respiratory depression[d]; Pulmonary embolism[e]; Hiccups[e]; Bronchospasm[d]; Dyspnoea[d] |
| ***Gastrointestinal disorders*** | ***Not Known*** | Peptic ulcer[b,e]; Gastric haemorrhage[e]; Intestinal perforation[e]; Pancreatitis[e]; |

| | | |
|---|---|---|
| | | Oesophagitis ulcerative[e]; Oesophagitis[e]; Oesophageal candidiasis; Abdominal pain[e]; Abdominal distension[e]; Diarrhoea[e]; Dyspepsia[e]; Nausea; Vomiting[d] |
| ***Hepatobiliary disorders*** | ***Not Known*** | Hepatitis; Increase of liver enzymes |
| ***Skin and subcutaneous tissue disorders*** | ***Not Known*** | Angioedema; Face oedema[d]; Petechiae[e]; Ecchymosis[e]; Skin atrophy[e]; Skin striae[e]; Skin hyperpigmentation[e]; Skin hypopigmentation[e]; Skin lesion[d]; Hirsutism[e]; Rash; Erythema[e]; Pruritus[e]; Urticaria; Acne[e]; Hyperhidrosis[e] |
| ***Musculoskeletal and connective tissue disorders*** | ***Not Known*** | Muscular weakness[e]; Osteonecrosis[e]; Pathological fracture[e]; Muscle atrophy[e]; Osteoporosis; Myopathy[e]; Neuropathic arthropathy[e]; Arthralgia; Growth retardation[e]; Myalgia[e]; Muscle twitching[d] |
| ***Reproductive system and breast disorders*** | ***Not Known*** | Menstruation irregular |
| ***General disorders and administration site conditions*** | ***Not Known*** | Injection site reaction[e]; Abscess sterile[e]; Impaired healing[e]; Oedema[d] Oedema peripheral[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[e]; Blood alkaline phosphatase increased[e]; Carbohydrate tolerance decreased[e]; Blood potassium |

| | | |
|---|---|---|
| | | decreased[e]; Urine calcium increased[e]; suppression of reactions to skin tests[a,e]; Blood urea increased[e] |
| ***Injury, poisoning and procedural complications*** | ***Not Known*** | Tendon rupture[e]; 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 CONTRAINDICATED AND 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

**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. Further traumatic episodes during that period may require special supportive therapy.

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.

*Lidocaine*
Symptoms of acute systemic toxicity
Central nervous system toxicity presents with symptoms of increasing severity. Patients may present initially with circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors or muscle twitching are more serious and precede the onset of generalized convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the

interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

Effects on the cardiovascular system may be seen in severe cases. Hypotension, bradycardia, arrhythmia and cardiac arrest may occur as a result of high systemic concentrations, with potentially fatal outcome.

Recovery occurs as a consequence of redistribution of the local anaesthetic drug from the central nervous system and metabolism and may be rapid unless large amounts of the drug have been injected.

Treatment of acute toxicity
If signs of acute systemic toxicity appear, injection of the anaesthetic should be stopped immediately.

Treatment will be required if convulsions and CNS depression occurs. The objectives of treatment are to maintain oxygenation, stop the convulsions and support the circulation. A patent airway should be established and oxygen should be administered, together with assisted ventilation (mask and bag) if necessary. The circulation should be maintained with infusions of plasma or intravenous fluids. Where further supportive treatment of circulatory depression is required, use of a vasopressor agent may be considered although this involves a risk of CNS excitation. Convulsions may be controlled by the intravenous administration of Diazepam or Thiopentone Sodium, bearing in mind that anti-convulsant drugs may also depress respiration and the circulation. Prolonged convulsions may jeopardize the patient's ventilation and oxygenation and early endotracheal intubation should be considered. If cardiac arrest should occur, standard cardiopulmonary resuscitation procedures should be instituted. Continual optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.

## 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. Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention. However the slower metabolism of the synthetic corticosteroid with their lower protein-bonding 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 methylprednisolone acetate. The average of the individual peak plasma concentrations was 14.8 ± 8.6 ng/ml, the average of the individual peak times was 7.25 ± 1.04 hours, and the average area under the curve (AUC) was 1354.2 ± 424.1 ng/ml x hrs (Day 1-21).

*Lidocaine:*
Pharmacokinetics of lidocaine after synovial absorption following intra-articular bolus injection in patients with knee joint arthroscopy was studied with different maximum concentration ($C_{max}$) values reported. The $C_{max}$ values are 2.18 µg/ml at 1 hour (serum) and 0.63 µg/ml at 0.5 hour (plasma) following administration of lidocaine doses of 7 mg/kgand 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.

*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-hydorxy-2,6-dimethylaniline metabolite.

Special Population

*Methylprednisolone*

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

*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.

**5.3 Preclinical safety data**

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

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, methylprednisolone sulfonate, which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* at 250 to 2,000 µg/plate, or in a mammalian cell gene mutation assay using Chinese hamster ovary cells at 2,000 to 10,000 µg/ml. Methylprednisolone suleptanate did not induce unscheduled DNA synthesis in primary rat hepatocytes at 5 to 1,000 µg/ml. Moreover, a review of published data indicates that prednisolone farnesylate (PNF), which is structurally similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* and *Escherichia coli* strains at 312 to 5,000 µg/plate. In a Chinese hamster fibroblast cell line, PNF produced a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested 1,500 µg/ml.

Reproductive toxicity
Corticosteroids have been shown to reduce fertility when administered to rats.
Male rats were administered corticosterone at doses of 0, 10, and 25 mg/kg/day by subcutaneous injection once daily for 6 weeks and mated with untreated females. The high dose was reduced to 20 mg/kg/day after Day 15. Decreased copulatory plugs were observed, which may have been secondary to decreased accessory organ weight. The numbers of implantations and live foetuses were reduced.

In reproductive studies, glucocorticoids such as methylprednisolone were shown to increase the incidence of malformations (cleft palate, central nervous system and skeletal anomalies) and embryo-foetal lethality (e.g., increase in resorptions) in many species. The relevance of these findings to the risk of malformations in human infants born to mothers treated with methylprednisolone early in pregnancy is unknown.

*Lidocaine:*
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.

Non-clinical data based on acute and sub-acute toxicity studies revealed no findings other than those attributable to either methylprednisolone or lidocaine alone.

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
Sodium chloride
Miripirium chloride
Benzyl alcohol (E1519)
Water for injections
Sodium hydroxide
Hydrochloric acid

### 6.2 Incompatibilities

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

### 6.3 Shelf life

Unopened: 2 years
Once opened, use immediately.

### 6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Keep the vials in the outer carton in order to protect from light.

### 6.5 Nature and contents of container

Type I flint glass vials with a butyl rubber cap. Each vial contains 2 ml of suspension.

Vials packed singly and in 10 vial packs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

**7 MARKETING AUTHORISATION HOLDER**

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA0822/123/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 02 March 1981

Date of last renewal: 28 January 2006

**10 DATE OF REVISION OF THE TEXT**

July 2023
Ref: DML 22_0 2ml IE