Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Depo-Medrone 40 mg/ml Suspension for Injection 1 ml vial

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolone acetate 40 mg/ml.
Each 1 ml vial contains 40mg methylprednisolone acetate.

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 is used in the management of corticosteroid disorders.

4.2 Posology and method of administration

Depo-Medrone may be used by any of the following routes: intramuscular, intra-articular, intralesional, intrarectal, intrabursal, periarticular or into the tendon sheath. It **must not** be used by the intrathecal or intravenous routes (see section 4.3).

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

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

The following may serve as a guide:

Adults: The usual dose is 20 to 120 mg daily or weekly, with adjustment on the basis of the individual requirements of the patient.

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).

Paediatric population: Dosage depends principally on the condition and to a lesser extent on body weight and age of the patient.

Intramuscular: For sustained systemic effect:
- Allergic conditions (asthma, drug reactions); 80 – 120 mg (2 – 3 ml).
- Dermatological conditions; 40 – 120 mg (1 – 3 ml).
- Rheumatic disorders, collagen disease, SLE; 40 – 120 mg (1 – 3 ml) per week.
- Adrenogenital syndrome; 40 mg (1 ml) every two weeks.

On average the effect of a single 2 ml (80 mg) injection may be expected to last approximately two weeks.

Intra-articular: Rheumatoid arthritis, osteo-arthritis. The dose of Depo-Medrone depends upon 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).

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

Intralesional: Keloids, localized lichen planus and simplex, granuloma annulare, alopecia areata, and discoid lupus erythematosus. For administration directly into the lesion for local effect in dermatological conditions; 20 – 60 mg (0.5 – 1.5 ml). For large lesions, the dose may be distributed by repeated local injections of 20 – 40 mg (0.5 – 1 ml). One to four injections are usually employed. Care should be taken to avoid injection of sufficient material to cause blanching, since this may be followed by a small slough.

Rectal: Ulcerative colitis; 40 – 120 mg (1 – 3 ml). Administer in retention enemas or by continuous drip in 30 – 300 ml of water, three to seven times weekly for two or more weeks.

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

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.

Special precautions should be observed when administering Depo-Medrone. Intramuscular injections should be made deeply into the gluteal muscles. The usual technique of aspirating prior to injection should be employed to avoid intravascular administration. Doses recommended for intramuscular injection must not be administered superficially or subcutaneously.

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. 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. 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 a wheal at the site made with 1 percent procaine hydrochloride solution. 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 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.

The usual sterile precautions should be observed with each injection.

4.3 Contraindications

Depo-Medrone is contraindicated:

- in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in patients who have systemic infection unless specific anti-infective therapy is employed.
- for use by the intrathecal route (due to its potential for neurotoxicity).
- for use by the epidural route of administration (see section 4.8).
- for use by the intravenous route.

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

4.4 Special warnings and precautions for use

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

Depo-Medrone vials are intended for single dose use only. Any multi-dose use of the product may lead to contamination.

Depo-Medrone is contraindicated for epidural, intranasal, intra-ocular, or any other unapproved route of administration (see section 4.8 for details of side effects reported from some non-recommended routes of administration). Severe medical events have been reported in association with the intrathecal/epidural routes of administration which are contraindicated (see sections 4.3 and 4.8). Appropriate measures must be taken to avoid intravascular injection.

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

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 minimise the incidence of dermal and sub-dermal 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 and intramuscular injection should include precautions against injection or leakage into the dermis. Injection into the deltoid muscle should be avoided because of a high incidence of subcutaneous atrophy.

Intralesional doses should not be placed too superficially, particularly in easily visible sites in patients with deeply pigmented skins, since there have been rare reports of subcutaneous atrophy and depigmentation.

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

Adrenal cortical atrophy develops during prolonged therapy and may persist for months after stopping treatment. 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. If corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

The following precautions apply for parenteral corticosteroids:
Following intra-articular injection, the occurrence of a marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted.

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.

The slower rate of absorption by intramuscular administration should be recognised.

Immunosuppressant effects/increased susceptibility to infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, exacerbate existing infections, increase the risk of reactivation or exacerbation of latent infections and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial

infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Do not use intra-synovially, intrabursally or in the tendon sheath for local effect in the presence of acute infection.

Monitor for the development of infection and consider withdrawal of corticosteroids or dosage reduction as needed.

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.

The use of Depo-Medrone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen. If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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

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. This effect may be minimized by use of alternate-day therapy.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

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.

Thyrotoxic Periodic Paralysis (TPP) can occur in patients with hyperthyroidism and with methylprednisolone-induced hypokalaemia.

TPP must be suspected in patients treated with methylprednisolone presenting signs or symptoms of muscle weakness, especially in patients with hyperthyroidism.

If TPP is suspected, levels of blood potassium must be immediately monitored and adequately managed to ensure the restoration of normal levels of blood potassium.

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
Potentially severe psychiatric adverse reactions may occur with systemic steroids. 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.

Psychological effects have been reported upon withdrawal of corticosteroid; the frequency is unknown. Patients/caregivers should be encouraged to seek medical advice if worrying psychological symptoms develop, 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. 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. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

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

Hepatobiliary effects
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.

Investigations
Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

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

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.

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.

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 may 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.

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).

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with malignancies, including haematological malignancies and solid tumours, following the use of systemic corticosteroids alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumours that have a high proliferative rate, high tumour burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

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

Depo-Medrone contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Paediatric population
Corticosteroids cause growth retardation in infancy, childhood and adolescence which may be irreversible. Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Treatment should be limited to the minimum dosage for the shortest possible time. The use of such a regimen should be restricted to the 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

2. Drugs that induce hepatic enzymes, such as rifampicin (antibiotic CYP3A4 inducer), rifabutin, carbamazepine (anticonvulsant CYP3A4 inducer and substrate), phenobarbitone and phenytoin (anticonvulsants CYP3A4 inducers), primidone and aminoglutethimide (aromatase inhibitor) enhance the metabolism of corticosteroids and its therapeutic effects may be reduced. Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

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

4. Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (see section 4.4).
Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.
The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

5. Oral anticoagulants (Vitamin K antagonists and non-vitamin K antagonists): The effect of the concomitant use of methylprednisolone with oral anticoagulants could vary. 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 (see section 4.4).
There are also reports of diminished effects of these anticoagulants when given concurrently with corticosteroids.

6. There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs.
Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.Salicylates and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothrombinaemia.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 substantial doses of 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.

Breast-feeding
Methylprednisolone is excreted in breast milk and infants of mothers treated with corticosteroids should be monitored carefully for signs of adrenal suppression.

Corticosteroids distributed into breast milk may interfere with endogenous glucocorticoid production in nursing infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylprednisolone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No human data on the effect of methylprednisolone on fertility are available. 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 machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The incidence of predictable undesirable side-effects associated with the use of corticosteroids, including HPA suppression, correlates with the relative potency of the drug, dosage, timing of administration and duration of treatment (see section 4.4).
Frequency not known: frequency cannot be estimated from the available data.

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Infections and infestations	***Not Known***	Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs); Opportunistic infection; Injection site infection; Peritonitis[#]; 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
Blood and lymphatic system disorders	***Not Known***	Leukocytosis
Endocrine disorders	***Not Known***	Cushingoid; Hypothalamic pituitary adrenal axis suppression; Withdrawal symptoms (too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see section 4.4). A 'withdrawal syndrome' 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; Glucose tolerance impaired; Sodium retention; Fluid retention; Increased requirements for insulin (or oral hypoglycemic agents in diabetics); Alkalosis hypokalaemic; Dyslipidaemia; Increased appetite (which may result in weight increase); Lipomatosis
Psychiatric disorders	***Not Known***	Affective disorder (including depressed mood, euphoric mood, affect lability, drug dependence, suicidal ideation); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behaviour; Insomnia; Irritability. The following events were most common in children: Mood swings; Abnormal behaviour; Insomnia; Psychotic disorder (including mania, delusion, hallucination, and Schizophrenia [aggravation of])
Nervous system disorders	***Not Known***	Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]); Seizure; Amnesia; Cognitive disorder; Dizziness; Headache; Epidural lipomatosis
Eye disorders	***Not Known***	Cataract; Glaucoma; Exophthalmos; Rare instances of blindness associated with intralesional therapy around the face and head [not a MedDRA PT]; Increased intra-ocular pressure, with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease; Chorioretinopathy; Vision blurred
Ear and labyrinth disorders	***Not Known***	Vertigo
Cardiac disorders	***Not Known***	Cardiac failure congestive (in susceptible patients)
Vascular disorders	***Not Known***	Hypertension; Hypotension; Embolism arterial; Thrombotic events; Flushing
Respiratory, thoracic and mediastinal disorders	***Not Known***	Pulmonary embolism; Hiccups
Gastrointestinal disorders	***Not Known***	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage); Gastric haemorrhage; Intestinal perforation; Pancreatitis; Oesophagitis ulcerative; Oesophagitis; Oesophageal candidiasis; Abdominal pain; Abdominal distension; Diarrhoea; Dyspepsia; Nausea
Hepatobiliary disorders	***Not Known***	Hepatitis; Increase of liver enzymes
Skin and subcutaneous	***Not Known***	Ecchymosis; Acne; Angioedema; Petechiae; Skin atrophy; Skin striae; Skin hyperpigmentation; Skin hypopigmentation; Hirsutism; Rash; Erythema; Pruritus; Urticaria; Hyperhidrosis;

tissue disorders		Panniculitis*
Musculoskeletal and connective tissue disorders	***Not Known***	Growth retardation; Osteoporosis; Muscular weakness; Osteonecrosis; Pathological fracture; Muscle atrophy; Myopathy; Neuropathic arthropathy; Arthralgia; Myalgia; Post injection pain flare (following intra-articular, periarticular, and tendon sheath injections)[a]
Reproductive system and breast disorders	***Not Known***	Menstruation irregular
General disorders and administration site conditions	***Not Known***	Impaired healing; Oedema peripheral; Injection site reaction; Abscess sterile; Fatigue; Malaise
Investigations	***Not Known***	Blood potassium decreased; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood alkaline phosphatase increased; Carbohydrate tolerance decreased; Urine calcium increased; suppression of reactions to skin tests [not a MedDRA PT]; Blood urea increased; Nitrogen balance negative (due to protein catabolism)
Injury, poisoning and procedural complications	***Not Known***	Tendon rupture (particularly of the Achilles tendon); Spinal compression fracture. Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury.

[a] Not a MedDRA Preferred term.
Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).
* Few cases of panniculitis have been reported following dose reduction or discontinuation of therapy, especially after long-term, high-dose treatment. Panniculitis is more common in paediatric patients than in adults, and most cases resolve spontaneously.

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. The frequency of these adverse reactions is not known.

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

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC Code: H02AB04

Methylprednisolone acetate is a synthetic glucocorticoid. It has greater anti-inflammatory potency than prednisolone and less tendency than prednisolone to induce sodium and water retention. An aqueous suspension may be injected directly into joints and soft tissues in the treatment of rheumatoid arthritis, osteoarthritis, bursitis and similar inflammatory conditions. For prolonged systemic effect it may be administered intramuscularly.

5.2 Pharmacokinetic properties

Absorption
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).

Distribution
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%.

Metabolism
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.

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

5.3 Preclinical safety data

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

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

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

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 3350
Sodium chloride
Miripirium chloride
Sodium hydroxide
Hydrochloric acid
Water for injections

6.2 Incompatibilities

None stated.

6.3 Shelf life

Unopened: 5 years
Once opened, use immediately.

6.4 Special precautions for storage

Do not store above 25ºC. Do not freeze.
Keep the vial in the outer carton.

6.5 Nature and contents of container

Type I flint glass vial with a butyl rubber plug and metal seal.
Each vial contains 1 ml of Depo-Medrone 40 mg/ml.

Vials packed singly and in 10 vial packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Depo-Medrone should not be mixed with any other fluid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever suspension and container permit.
Shake well before use.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland Unlimited Company
The Watermarque Building
Ringsend Road
Dublin 4
D04 K7N3

Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/122/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 28 January 2006

10 DATE OF REVISION OF THE TEXT

December 2025