SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Depo-Medrone 40 mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolone acetate 40 mg/ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for Injection.
White, sterile, white aqueous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Depo-Medrone may be used locally or systemically, particularly where oral therapy is not feasible.

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

Intramuscular administration:

1. Rheumatic disorders
   Rheumatoid arthritis

2. Collagen diseases/arteritis
   Systemic lupus erythematosus

3. Dermatological diseases
   Severe erythema multiforme (Stevens-Johnson syndrome)

4. Allergic states
   Bronchial asthma
   Drug hypersensitivity reactions
   Angioneurotic oedema

5. Gastro-intestinal diseases
   Ulcerative colitis
   Crohn's disease

6. Respiratory diseases
   Fulminating or disseminated tuberculosis (with appropriate antituberculous chemotherapy)
   Aspiration of gastric contents

7. Miscellaneous
   TB meningitis (with appropriate antituberculous chemotherapy)

Intra-articular administration:
Rheumatoid arthritis
Osteo-arthritis with an inflammatory component

Soft tissue administration (intrabursal, periarticular, into tendon sheath):
Synovitis not associated with infection
Epicondylitis
Tenosynovitis
Plantar fasciitis
Bursitis

Intralesional:
Keloids
Localized lichen planus
Localized lichen simplex
Granuloma annulare
Discoid lupus erythematosus
Alopecia areata

4.2 Posology and method of administration

Depo-Medrone should not be mixed with any other suspending agent or solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever suspension and container permit. Depo-Medrone may be used by any of the following routes: intramuscular, intra-articular, periarticular, intrabursal, intralesional 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 vials are intended for single dose use only.

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 and collagen diseases (rheumatoid arthritis, SLE), 40 – 120 mg (1 – 3 ml) per week.

Dosage must be individualized and depends on the condition being treated and its severity.

The frequency of intramuscular injections should be determined by the duration of clinical response.

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, localised lichen planus, localized lichen 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.

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

Into the tendon sheath: 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 per cent 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 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.

Paediatric population:
Dosage may 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.

Elderly:
When used according to instructions, there is no information to suggest that a change in dosage is warranted in the elderly. However, treatment of elderly patients, 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 Special warnings and special precautions for use).

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, 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

Warnings and Precautions:
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 multidose use of the product may lead to contamination.

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

Due to the absence of a true tendon sheath, the Achilles tendon should not be injected with Depo-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. 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 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. In patients who have received more than physiological doses of systemic corticosteroids (approximately 6 mg methylprednisolone) for greater than 3 weeks, withdrawal should not be abrupt. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 6 mg methylprednisolone is reached, dose reduction should be slower to allow the HPA-axis to recover.

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

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

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

Corticosteroids should not be injected into unstable joints.

Sterile technique is necessary to prevent infections or contamination.

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, 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 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.

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.

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. Salt and/or a mineralocorticoid are only needed if mineralocorticoid secretion is impaired.

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Gastrointestinal Effects
High doses of corticosteroids may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis. In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

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

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

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

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
Patients should carry 'Steroid Treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

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

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

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

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

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.

Depo-Medone 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

CYP3A4 SUBSTRATES – In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments

required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with co-administration.

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

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

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.

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

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

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

toxicity. 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:
1) Indinavir, ritonavir and pharmacokinetic enhancers (cobicistat) (CYP3A4 inhibitors and substrates) may increase plasma concentrations of corticosteroids.
2) 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.

4.6 Fertility, pregnancy and lactation

4.6 Fertility, pregnancy and lactation

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

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

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the

neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. Although neonatal adrenal insufficiency appears to be rare in infants who were exposed in utero to corticosteroids, those exposed to substantial doses of corticosteroids must be carefully observed and evaluated for signs of adrenal insufficiency. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state. However, corticosteroids do not appear to cause congenital anomalies when given to pregnant women.

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

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

Breast-feeding
Corticosteroids are excreted in small amounts in breast milk, however, doses of up to 40 mg daily of methylprednisolone are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses than this may have a degree of adrenal suppression, but the benefits of breast-feeding are likely to outweigh any theoretical risk.

Corticosteroids distributed into breast milk may interfere with endogenous glucocorticoid production in nursing infants. This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**

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
Blood and lymphatic system disorders	***Not Known***	Leukocytosis
Immune system disorders	***Not Known***	Drug hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction
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 increased); Lipomatosis
Psychiatric disorders	***Not Known***	Affective disorder (including Depressed mood, Euphoric mood, Affect lability, Drug dependence, Suicidal ideation). The following events were most common in children: Mood swings; Abnormal behaviour; Insomnia; Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia [aggravation of]); Confusional state; Mental disorder; Anxiety; Personality change; Mood swings; Abnormal behaviour; Insomnia; Irritability (children and adults)
Nervous system disorders	***Not Known***	Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]); Seizure; Amnesia; Cognitive disorder; Dizziness; Headache

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Eye disorders	***Not Known***	Cataract; Glaucoma; Exophthalmos; Vision blurred (see also section 4.4); Chorioretinopathy; rare instances of blindness associated with intralesional therapy around the face and head*; Increased intra-ocular pressure, with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease
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; Abdominal pain; Abdominal distension; Diarrhoea; Dyspepsia; Nausea
Hepatobiliary disorders	***Not known***	Hepatitis, Increase of liver enzymes
Skin and subcutaneous tissue disorders	***Not Known***	Angioedema; Hirsutism; Petechiae; Ecchymosis; Skin atrophy; Erythema; Hyperhidrosis; Skin striae; Skin hyperpigmentation; Rash; Pruritus; Urticaria; Acne; Skin hypopigmentation
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)*
Reproductive system and breast disorders	***Not Known***	Menstruation irregular
General disorders and administration site conditions	***Not Known***	Abscess sterile; Impaired healing; Oedema peripheral; Fatigue; Malaise; Injection site reaction

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
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*; Blood urea increased
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.

† Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data).
* Not a MedDRA PT.
#Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).

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 disturbance.

Extradural: Wound dehiscence, loss of sphincter control.

Intranasal: Permanent/temporary blindness, rhinitis.

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

Miscellaneous injection sites: 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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. In such event the patient may require to be supported during any further traumatic episode.

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

Methylprednisolone is dialysable.

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 Depo-Medrone. 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.

Methylprednisolone acetate is less soluble than methylprednisolone.

5.3 Preclinical safety data

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

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene glycol
Sodium chloride
Myristyl-gamma-picolinium chloride
Water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

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, 2 ml, or 3 ml of Depo-Medrone 40 mg/ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Depo-Medrone should not be mixed with any other fluid. Discard any remaining suspension after use.

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road,
Sandwich,
Kent CT13 9NJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00057/0963

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 March 1989

Date of latest renewal: 5 September 1996

10 DATE OF REVISION OF THE TEXT

22/01/2024