SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medrol 4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg methylprednisolone.

Excipients with known effect:
lactose, sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anti-allergic, anti-inflammatory for treatment of allergic conditions such as asthma and diverse skin disease, inflammatory states and arthritis.

4.2 Posology and method of administration

The initial dosage of methylprednisolone tablets may vary depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. Clinical situations in which high-dose therapy may be indicated include multiple sclerosis (200 mg/day), cerebral edema (200-1,000 mg/day), and organ transplantation (up to 7 mg/kg/day). If after a reasonable period of time there is a lack of satisfactory clinical response, methylprednisolone tablets should be discontinued and the patient transferred to other appropriate therapy. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.
After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of methylprednisolone tablets for a period of time consistent with the patient's condition.
It should be emphasized that dosage requirements are variable and must be individualized on the basis of the disease under treatment and the response of the patient.
Alternate Day Therapy (ADT)
Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticosteroid is administered every other morning. The purpose of this mode of therapy is to provide a patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimizing certain

undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms, and growth suppression in children.

4.3 Contraindications

Methylprednisolone tablets are contraindicated:

- in patients who have systemic fungal infections
- in patients who have systemic infections unless specific anti-infective therapy is employed
- in patients who have hypersensitivity to the active substance or to any of the excipients listed in section 6.1

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

4.4 Special warnings and precautions for use

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.

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. Chicken pox 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 immunoglobulin (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.

Exposure to measles should be avoided. Medical advice must be sought immediately if exposure occurs. Prophylaxis with normal intramuscular immunoglobulin may be needed.

Similarly corticosteroids should be used with great care in patients with known or suspected parasitic infections such as Strongyloides (threadworm) infestation, which may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. The antibody response to other vaccines may be diminished.

The use of corticosteroids 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 have suggested that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality.

Immune System
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 allergy to any drug.

This medicine contains lactose produced from cow's milk. Caution should be exercised in patients with a known or suspected hypersensitivity to cow's milk or its components or other dairy products because it may contain trace amounts of milk ingredients.

Endocrine Effects
In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.

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.

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. In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

- Patients receiving doses of systemic corticosteroid greater than 32 mg daily of methylprednisolone.
- Patients repeatedly taking doses in the evening.

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.

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

Particular care is required when considering the use of systemic corticosteroids in patients with hypothyroidism and frequent patient monitoring is necessary.

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

Particular care is required when considering the use of systemic corticosteroids in patients with Diabetes mellitus (or a family history of diabetes) and frequent patient monitoring is necessary.

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 also section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

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

Nervous System Effects
Particular care is required when considering the use of systemic corticosteroids in patients with seizure disorders and myasthenia gravis (see myopathy statement in Musculoskeletal Effects section) and frequent patient monitoring is necessary.

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.

Particular care is required when considering the use of systemic corticosteroids in patients with glaucoma (or a family history of glaucoma) and ocular herpes simplex as there is a fear of corneal perforation, and frequent patient monitoring is necessary.

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.

Secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

Cardiac Events
Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia 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. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

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

Particular care is required when considering the use of systemic corticosteroids in patients with recent myocardial infarction (myocardial rupture has been reported) and frequent patient monitoring is necessary.

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

Vascular Effects
Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

Hypertension
Predisposition to thrombophlebitis

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.

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

Peptic ulceration.
Fresh intestinal anastomoses.
Abscess or other pyogenic infections.
Ulcerative colitis.
Diverticulitis.

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.

Hepatobiliary Effects
Particular care is required when considering the use of systemic corticosteroids in patients with liver failure or cirrhosis and frequent patient monitoring is necessary.

Rarely hepatobiliary disorders were reported, in the majority of these cases, they were reversible after withdrawal of therapy. Therefore appropriate monitoring is required.

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. Cases of rhabdomyolysis have been reported. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Particular care is required when considering the use of systemic corticosteroids in patients with osteoporosis (post-menopausal females are particularly at risk) and frequent patient monitoring is necessary.

Renal and Urinary
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.

Particular care is required when considering the use of systemic corticosteroids in patients with renal insufficiency and frequent patient monitoring is necessary.

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

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose or whenever possible as a single morning dose on alternative days. Frequent patient review is required to appropriately titrate the dose against disease activity (see section 4.2).

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 non-steroidal 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.

Paediatric population: Corticosteroids cause growth retardation in infancy, childhood and adolescence. 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. In order to minimise suppression of the hypothalamo-pituitary-adrenal axis and growth retardation, treatment should be administered where possible as a single dose on alternate days (see section 4.2).

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.

High doses of corticosteroids may produce pancreatitis in children.

Use in the elderly: The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

Ingredient warning
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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 CYP3A4 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.

Drug Class or Type - DRUG or SUBSTANCE	**Interaction**	**Effect**
Antibiotic, Antitubercular - RIFAMPIN - RIFABUTIN	CYP3A4 Inducer	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.
Anticonvulsants - PHENOBARBITAL - PHENYTOIN - PRIMIDONE		
Anticonvulsant - CARBAMAZEPINE	CYP3A4 Inducer (and Substrate)	CYP3A4 INDUCERS – see box above 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.
Macrolide Antibacterial - TROLEANDOMYCIN	CYP3A4 Inhibitor	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.
- GRAPEFRUIT JUICE		
Calcium Antagonist - MIBEFRADIL		
Histamine H_2 receptor Antagonist - CIMETIDINE		
Antibacterial - ISONIAZID		In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 Inhibitor (and Substrate)	CYP3A4 INHIBITORS – see box above 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
Antifungal - ITRACONAZOLE - KETOCONAZOLE		

Calcium Channel Blocker - DILTIAZEM		co-administration. (1) Mutual inhibition of metabolism occurs with concurrent use of ciclosporin and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon co-administration. (2) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. (3) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.
Contraceptives (oral) - ETHINYLESTRADIOL/ NORETHINDRONE		
Immunosuppressant - CICLOSPORIN (1)		
Macrolide Antibacterial - CLARITHROMYCIN - ERYTHROMYCIN		
Antivirals - HIV-PROTEASE INHIBITORS (2) (3) Pharmacokinetic enhancers -COBICISTAT		
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 Substrate	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.
NSAIDs (nonsteroidal anti-inflammatory drugs) (4) - high-dose ASPIRIN (5) (acetylsalicylic acid)	Non-CYP3A4-mediated effects	(4) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. (5) 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.

Anticholinergics (6) - NEUROMUSCULAR BLOCKERS (7)		(6) 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 Musculoskeletal, for additional information.) (7) 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.
Anticholinesterases		Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Anti-diabetics		Because corticosteroids may increase blood glucose concentrations, dosage adjustments of anti-diabetic agents may be required.
Anticoagulants (oral) VITAMIN K ANTAGONISTS		The effect of methylprednisolone on vitamin K antagonists (e.g., warfarin, acenocoumarol, fluindione) is variable. There are reports of enhanced as well as diminished effects of these anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored (e.g. INR or prothrombin time) to maintain the desired anticoagulant effects.
Potassium-depleting agents		When corticosteroids are administered concomitantly with potassium-depleting agents (i.e. diuretics), patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthenes, or beta2 agonists.
Aromatase inhibitors -AMINOGLUTETHIMIDE		Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

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. 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 effects 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. Infants born to mothers, who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important.

Since adequate human reproductive studies have not been done with methylprednisolone, this medicinal product, as with all drugs, should be used in pregnancy only after a careful assessment of the benefit-risk ratio to the mother, embryo, foetus or child. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

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

System Organ Class	Frequency†	Undesirable Effects
Infections and infestations	***Common***	Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs)
	Not Known	Opportunistic infection; recurrence of dormant tuberculosis, Peritonitis†
Blood and lymphatic system disorders	***Not Known***	Leukocytosis
Immune system disorders	***Not Known***	Drug hypersensitivity Anaphylactic reaction Anaphylactoid reaction
Endocrine disorders	***Common***	Cushingoid
	Not Known	Hypothalamic pituitary adrenal axis suppression
Neoplasms benign, malignant and unspecified (including cysts and polyps)	***Not Known***	Kaposi's sarcoma
Metabolism and nutrition disorders	***Common***	Sodium retention; Fluid retention
	Not Known	Metabolic acidosis ;Alkalosis hypokalaemic; Dyslipidaemia; Glucose tolerance impaired; increased requirements for insulin (or oral hypoglycemic agents in diabetics); Lipomatosis;; Increased appetite (which may result in Weight increased); Epidural lipomatosis
Psychiatric disorders	***Common***	Affective disorder (including Depressed mood and Euphoric mood)
	Not Known	Psychotic disorder (including Mania, Delusion, Hallucination, and Schizophrenia; Psychotic behaviour; Affective disorder (including Affect lability, Psychological dependence, Suicidal ideation); Mental disorder; Personality change; Confusional state; Anxiety; Mood swings; Abnormal behaviour; Insomnia; Irritability
Nervous system disorders	***Not Known***	Intracranial pressure increased (with Papilloedema [Benign intracranial hypertension]); Seizure; Amnesia; Cognitive disorder; Dizziness; Headache
Eye disorders	***Common***	Cataract
	Rare	Vision blurred (see also section 4.4)
	Not Known	Glaucoma; Exophthalmos; Corneal thinning; Scleral thinning; Chorioretinopathy
Ear and labyrinth disorders	***Not Known***	Vertigo
Cardiac disorders	***Not Known***	Cardiac failure congestive (in susceptible patients); Myocardial rupture following myocardial infarction
Vascular disorders	***Common***	Hypertension

	Not Known	Hypotension; Embolism arterial; Thrombotic events; Flushing
Respiratory, thoracic and mediastinal disorders	***Not Known***	Pulmonary embolism, Hiccups
Gastrointestinal disorders	***Common***	Peptic ulcer (with possible Peptic ulcer perforation and Peptic ulcer haemorrhage)
	Not Known	Intestinal perforation; Gastric haemorrhage; Pancreatitis; Oesophagitis ulcerative; Oesophagitis;Abdominal distension; Abdominal pain; Diarrhoea; Dyspepsia; Nausea
Hepatobiliary disorders	***Not Known***	Increase of liver enzymes (e.g alanine aminotransferase increased, aspartate aminotransferase increased)
Skin and subcutaneous tissue disorders	***Common***	Skin atrophy; Acne
	Not Known	Angioedema; Hirsutism; Petechiae; Ecchymosis; Erythema; Hyperhidrosis; Skin striae; Rash Pruritus; Urticaria; Telangiectasia; Panniculitis[#]
Musculoskeletal and connective tissue disorders	***Common***	Muscular weakness; Growth retardation
	Not Known	Myalgia; Myopathy; Rhabdomyolysis; Muscle atrophy; Osteoporosis; Osteonecrosis; Pathologic fracture; Neuropathic arthropathy; Arthralgia;
Reproductive system and breast disorders	***Not Known***	Menstruation irregular
General disorders and administration site conditions	***Common***	Impaired healing
	Not Known	Oedema peripheral ;Fatigue; Malaise; Withdrawal symptoms - too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death (see section 4.4)
Investigations	***Common***	Blood potassium decreased
	Not Known	Intraocular pressure increased; Carbohydrate tolerance decreased; Urine calcium increased Blood alkaline phosphatase increased; Blood urea increased; Suppression of reactions to skin tests[*]
Injury, poisoning and procedural complications	***Not Known***	Tendon rupture (particularly of the Achilles tendon); Spinal compression fracture

***** 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)

[#] Panniculitis may occur following dose reduction or discontinuation of methylprednisolone and has been more frequently reported in the paediatric population.

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)

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).

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

4.9 Overdose

Administration of methylprednisolone should not be discontinued abruptly but tailed off over a period of time. Appropriate action should be taken to alleviate the symptoms produced by any side-effect that may become apparent. It may be necessary to support the patient with corticosteroids during any further period of trauma occurring within two years of overdosage.

There is no clinical syndrome of acute overdose with methylprednisolone. Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. Methylprednisolone is haemodialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticosteroids, ATC Code H02AB04

Methylprednisolone is a synthetic glucocorticoid and a methyl derivative of prednisolone.
Methylprednisolone is a potent anti-inflammatory agent with the capacity to profoundly inhibit the immune system.

Glucocorticoids act primarily by binding to and activating intracellular glucocorticoid receptors. Activated glucocorticoid receptors bind to promoter regions of DNA (which may activate or suppress transcription) and activate transcription factors resulting in inactivation of genes through de-acetylation of histones.

Following corticosteroid administration there is a delay of several hours for the clinical effects resulting from changes in gene expression to be seen.
Other effects not related to gene expression may be more immediate.

Corticosteroids influence the kidney and fluid and electrolyte balance, lipid, protein, and carbohydrate metabolism, skeletal muscle, the cardiovascular system, the immune system, the nervous system, and the endocrine system. Corticosteroids are also critical in the maintenance of function during stress.

5.2 Pharmacokinetic properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Absorption:
Methylprednisolone is rapidly absorbed and the maximum plasma methylprednisolone concentration is achieved around 1.5 to 2.3 hours across doses following oral administration in normal healthy adults. The absolute bioavailability of methylprednisolone in normal healthy subjects is generally high (82% to 89%) following oral administration.

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:
Corticosteroids are metabolised mainly in the liver but also in the kidney and are excreted in the urine.

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 enzyme. (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.

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 repeated-dose studies were those expected to occur with continued exposure to exogenous adrenocortical steroids.

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.

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.

Reproductive toxicity:
Methylprednisolone has not been evaluated in animal fertility studies. 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 fetuses 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 or 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
Lactose monohydrate**,** Maize starch**,** Sucrose**,** Calcium stearate**.**

6.2 Incompatibilities
Not applicable.

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

6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
Medrol tablets are packaged in clear PVC/Aluminum blister packs of 30 tablets.

6.6 Special precautions for disposal and other handling
No special requirements.

7. LICENSE HOLDER

Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya, 4672509.

8. LICENSE NUMBER

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