SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

MEDROL® 4 mg tablets

MEDROL® 16 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MEDROL 4 mg tablet contains 4 mg methylprednisolone.

Each MEDROL 16 mg tablet contains 16 mg methylprednisolone.

Contains sugar (lactose monohydrate and sucrose).

Excipients with known effect

Each MEDROL 4 mg tablet contains 80,0 mg lactose monohydrate and 1,50 mg sucrose.

Each MEDROL 16 mg tablet contains 159,0 mg lactose monohydrate and 2,80 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

MEDROL 4 mg: half oval, elliptical, white tablets, debossed with “MEDROL 4” on one side and double scored on the other.

MEDROL 16 mg: elliptic, convex, white tablets engraved with “MEDROL 16” on one side and a cross score on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Endocrine disorders

- Primary or secondary adrenocortical insufficiency in conjunction with mineralocorticoids
- Autoimmune thyroiditis

2. Corticosteroid responsive diseases including

2.1. Rheumatic disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation)

in cases of:

- Psoriatic arthritis
- Rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Ankylosing spondylitis
- Acute nonspecific tenosynovitis
- Acute and subacute bursitis
- Acute gouty arthritis

2.2. Collagen diseases

During exacerbation of, or as maintenance therapy in selected cases of:

- Systemic lupus erythematosus
- Acute rheumatic carditis

2.3. Dermatological diseases

- Pemphigus
- Exfoliative dermatitis
- Bullous dermatitis herpetiformis
- Mycosis fungoides
- Severe erythema multiforme

- Severe psoriasis

2.4. Allergic conditions

- Control of severe or incapacitating allergic conditions intractable to adequate treatment with conventional medicines
- Seasonal or perennial allergic rhinitis
- Serum sickness
- Bronchial asthma
- Angioedema
- Contact dermatitis
- Urticaria
- Atopic dermatitis

2.5. Ophthalmic diseases

Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as:

- Allergic corneal marginal ulcers
- Herpes zoster ophthalmicus
- Anterior segment inflammation
- Chorioretinitis
- Diffuse posterior uveitis and choroiditis
- Sympathetic ophthalmia
- Iritis and iridocyclitis
- Optical neuritis

2.6. Respiratory diseases

- Symptomatic sarcoidosis
- Eosinophilic pneumonia not manageable by other means
- Berylliosis
- Pulmonary emphysema where bronchospasm or bronchial oedema plays a significant role

2.7. Haematological disorders

- Idiopathic and secondary thrombocytopenia in adults
- Acquired (autoimmune) haemolytic anaemia
- Erythroblastopenia (RBC anaemia)
- Congenital (erythroid) hypoplastic anaemia

2.8. Neoplastic diseases

For palliative management of:

- Leukaemias and lymphomas in adults
- Acute leukaemia of childhood

2.9. Oedematous states

- To induce diuresis or remission of proteinuria in nephrotic syndrome without uraemia, or the idiopathic type, or that due to lupus erythematosus in conjunction with diuretic medicines, in cirrhosis of the liver with refractory ascites

2.10. Gastrointestinal diseases

To tide the patient over a critical period of the disease in:

- Ulcerative colitis
- Crohn's disease

3. Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate antituberculous chemotherapy
- Systemic dermatomyositis (polymyositis)

4.2 Posology and method of administration

The lowest possible dose of corticosteroid should be used to control the condition under treatment and when

reduction in dosage is possible, the reduction should be gradual.

Posology

The initial dosage of MEDROL may vary from 4 to 48 mg per day depending on the specific disease entity being treated. In cases of less severity, lower doses will generally suffice while in selected patients, higher doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, MEDROL should be discontinued and the patient transferred to other appropriate therapy.

IT SHOULD BE EMPHASISED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALISED ON THE BASIS OF THE DISEASE BEING TREATED AND THE RESPONSE OF THE PATIENT.

Once a favourable response is noted, the proper maintenance dosage should be determined by decreasing the initial medicine dosage in small increments 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 with regard to medicine dosage. Included in the situations which may require dosage adjustments are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual medicine responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity being treated; in this latter situation it may be necessary to increase the dosage of MEDROL for a period of time consistent with the patient's condition. If the medicine is stopped after long-term therapy, it is recommended that it be withdrawn gradually rather than abruptly.

Alternate day therapy (ADT)

ADT is a corticosteroid dosing regimen in which twice the usual daily dose of corticosteroid such as MEDROL is administered every other morning. The purpose of this mode of therapy is to provide the patient requiring long-term pharmacologic dose treatment with the beneficial effects of MEDROL while reducing the severity of certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms and growth suppression in children.

Method of administration

For oral use.

4.3 Contraindications

MEDROL tablets are contraindicated in patients with:

- known hypersensitivity to methylprednisolone or to any of the excipients listed in section 6.1
- systemic fungal infections
- traumatic brain injury

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 such as MEDROL may increase susceptibility to infection, may mask signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids such as MEDROL are used. Infections with any pathogen, including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids such as MEDROL alone or in combination with other immunosuppressive medicines that affect cellular immunity, humoral immunity, or neutrophil function. These infections can be severe and may be fatal. With increasing doses of MEDROL, the rate of occurrence of infectious complications increases.

Persons who are on medicines which suppress the immune system such as MEDROL 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 including MEDROL.

While on MEDROL therapy, patients should not be vaccinated against smallpox. Other immunisation procedures should not be undertaken in patients who are on MEDROL because of the possible hazards of

neurological complications and a lack of antibody response.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving MEDROL. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of MEDROL; however, the response to such vaccines may be diminished.

The use of MEDROL in active tuberculosis should be restricted to cases of fulminating or tuberculosis meningitis in conjunction with an appropriate antituberculous regimen.

The use of MEDROL in patients with latent tuberculosis may activate the tuberculosis. In patients with tuberculin reactivity, close observation is necessary, as reactivation of the disease may occur. During prolonged MEDROL therapy, these patients should receive chemoprophylaxis.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy such as MEDROL. Discontinuation of MEDROL 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, and a systematic review concluded that short-course, high-dose corticosteroids did not support 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

Hypersensitivity reactions (e.g. angioedema) may occur, including skin reactions and anaphylactic/anaphylactoid reactions. Appropriate precautionary measures should be taken prior to administration of MEDROL, especially when the patient has a history of allergy to any medicine.

Endocrine effects

In patients on MEDROL therapy of 2 to 3 weeks or more who are subjected to stress, increased dosage of corticosteroids before, during, and after the stressful situation may be indicated.

Corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). This effect may be minimised by the use of alternate-day therapy (see section 4.2, *Alternate day therapy*).

Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

MEDROL-induced adrenocortical insufficiency may be minimised by gradual reduction of dosage. This type of insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, MEDROL therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

A steroid “withdrawal syndrome” may also occur following abrupt discontinuance of glucocorticoids and may cause anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension.

Because glucocorticoids such as MEDROL can produce or aggravate Cushing’s syndrome, MEDROL should be avoided in patients with Cushing’s disease.

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

Metabolism and nutrition

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

Psychiatric effects

Psychic derangements may appear when corticosteroids including MEDROL are used, ranging from

euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids such as MEDROL.

Potentially severe psychiatric adverse reactions may occur with corticosteroids such as MEDROL (see section 4.8, *Psychiatric disorders*). Symptoms typically emerge within a few days or weeks of starting treatment. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary.

Psychological effects have been reported upon withdrawal of corticosteroids including MEDROL; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of MEDROL.

Nervous system effects

MEDROL should be used with caution in patients with seizure disorders.

MEDROL should be used with caution in patients with myasthenia gravis (see myopathy statement in Musculoskeletal section).

Although controlled clinical trials have shown corticosteroids including MEDROL to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids including MEDROL affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect (see section 4.2).

There have been reports of epidural lipomatosis in patients taking corticosteroids such as MEDROL, typically with long-term use at high doses. The onset of symptoms is usually gradual. The symptoms may include back pain and sensory or motor disorders.

Ocular effects

MEDROL should not be used in patients with ocular herpes simplex because of possible corneal perforation.

Prolonged use of corticosteroids including MEDROL 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. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids such as MEDROL.

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

Patients on repeated/prolonged courses of steroids should have regular ophthalmic examination/assessments.

Cardiac effects

Adverse effects of glucocorticoids including MEDROL on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects especially if high doses and prolonged courses are used. Accordingly, MEDROL 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 MEDROL should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Vascular effects

Thrombosis including venous thromboembolism has been reported to occur with corticosteroids including

MEDROL. As a result, MEDROL should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

MEDROL should be used with caution in patients with hypertension as MEDROL may further increase the blood pressure.

Gastrointestinal effects

High doses of MEDROL may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids such as MEDROL 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 such as MEDROL 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.

MEDROL should be used with caution in ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary effects

Particular care is required when considering the use of systemic corticosteroids such as MEDROL 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 including MEDROL, 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 medicines (e.g. pancuronium). This acute myopathy is generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping MEDROL may require weeks to years.

Osteoporosis is a common but insufficiently recognised adverse effect associated with a long-term use of glucocorticoid including MEDROL.

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 MEDROL. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

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

Investigations

Corticosteroids such as MEDROL can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. Dietary salt restriction and potassium supplementation may be necessary. Corticosteroids including MEDROL increase calcium excretion.

Injury, poisoning and procedural complications

MEDROL is contraindicated in treatment of traumatic brain injury; a multicentre study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered SOLU-MEDROL compared to placebo (see section 4.3).

Other

The lowest possible dose of MEDROL should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Aspirin and nonsteroidal anti-inflammatory drugs should be used cautiously in conjunction with MEDROL.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. MEDROL 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, including MEDROL, or in combination with other chemotherapeutic medicines. 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 medicines, should be monitored closely and appropriate precautions should be taken.

Excipients with known effect

MEDROL contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take MEDROL.

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

Paediatric population

Growth and development of infants and children on prolonged MEDROL therapy should be carefully observed.

Growth may be suppressed in children receiving long-term MEDROL therapy. Alternate day MEDROL therapy may avoid or minimise this side effect (see section 4.2, *Alternate day therapy*).

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

High doses of MEDROL may produce pancreatitis in children.

4.5 Interaction with other medicines and other forms of interaction

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

CYP3A4 inhibitors

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

CYP3A4 inducers

Medicines that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medicines that are substrates for CYP3A4. Co-administration may require an increase in MEDROL dosage to achieve the desired result.

CYP3A4 substrates

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

Non-CYP3A4-mediated effects

Other interactions and effects that occur with MEDROL are described in Table 1 below.

Table 1 provides a list and descriptions of the most common and/or clinically important medicine interactions or effects with MEDROL.

Table 1. Important medicine or substance interactions/effects with MEDROL

Medicine class or type **MEDICINE or SUBSTANCE**	**Interaction/effect**
Antibacterial - ISONIAZID	CYP3A4 INHIBITOR. In addition, there is a potential effect of MEDROL to increase the acetylation rate and clearance of isoniazid (see CYP3A4 inhibitors above for the results of the interaction).
Antibiotic, antitubercular - RIFAMPICIN	CYP3A4 INDUCER (see CYP3A4 inducers above for the results of the interaction).
Anticoagulants (oral) - WARFARIN	The effect of MEDROL on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.
Anticonvulsants - CARBAMAZEPINE	CYP3A4 INDUCER (and SUBSTRATE) (see CYP3A4 inducers and CYP3A4 substrates above for the results of the interaction).
Anticonvulsants - PHENOBARBITAL (PHENOBARBITONE) - PHENYTOIN	CYP3A4 INDUCERS (see CYP3A4 inducers above for the results of the interaction).
Anticholinergics - NEUROMUSCULAR BLOCKERS	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking medicines (see section 4.4, *Musculoskeletal*).

	2) Antagonism of the neuromuscular blocking effects of all competitive neuromuscular blockers.
Anticholinesterases	Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Antidiabetics	Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic medicines may be required.
Antiemetic - APREPITANT - FOSAPREPITANT	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Antifungal - ITRACONAZOLE - KETOCONAZOLE	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Antivirals - HIV-PROTEASE INHIBITORS	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction). 1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors, resulting in reduced plasma concentrations. Steroids are also known inducers of CYP enzymes in animal models and *in vitro* studies. Dexamethasone, at doses similar to those used in clinical practice, has been shown to increase CYP3A4 activity in both healthy volunteers and human hepatocyte cultures. Therefore, corticosteroids may induce the metabolism of HIV-protease inhibitors by upregulation of CYP3A4.
Aromatase inhibitors - AMINOGLUTETHIMIDE	Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

Calcium channel blocker - DILTIAZEM	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Contraceptives (oral) - ETHINYL ESTRADIOL/ NORETHINDRONE	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
- GRAPEFRUIT JUICE	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
Immunosuppressant - CICLOSPORIN	CYP3A4 INHIBITOR (and SUBSTRATE) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction). 1) Mutual inhibition of metabolism occurs with concurrent use of ciclosporin and MEDROL, which may increase the plasma concentrations of either or both medicines. Therefore, it is possible that adverse events associated with the use of either medicine alone may be more likely to occur upon co-administration. 2) Convulsions have been reported with concurrent use of MEDROL and ciclosporin.
Immunosuppressant - CYCLOPHOSPHAMIDE - TACROLIMUS	CYP3A4 SUBSTRATES (see CYP3A4 substrates above for the results of the interaction).
Macrolide antibacterial - CLARITHROMYCIN - ERYTHROMYCIN	CYP3A4 INHIBITORS (and SUBSTRATES) (see CYP3A4 inhibitors and CYP3A4 substrates above for the results of the interaction).
Macrolide antibacterial - TROLEANDOMYCIN	CYP3A4 INHIBITOR (see CYP3A4 inhibitors above for the results of the interaction).
NSAIDs (nonsteroidal anti-inflammatory-drugs)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with

- high-dose ASPIRIN (acetylsalicylic acid)	NSAIDs. 2) MEDROL may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of MEDROL treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.
Potassium-depleting medicines	When corticosteroids are administered concomitantly with potassium-depleting medicines (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, xanthines or beta2 agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been demonstrated. Adequate human reproductive studies have not been performed with methylprednisolone.

Animal studies have shown that corticosteroids such as MEDROL, when administered to the mother at high doses, may cause foetal malformations. There is no evidence that corticosteroids cause an increased incidence of congenital anomalies when given to pregnant women. However, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation.

MEDROL is teratogenic in animals.

Some corticosteroids readily cross the placenta and cause low birth weight in infants born of mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose related and may be minimised by administering lower MEDROL doses. 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 occur in neonates following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important.

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

Cataracts have been observed in infants born to mothers undergoing treatment with corticosteroids including MEDROL during pregnancy.

Breastfeeding

Safety of MEDROL in lactation has not been demonstrated. Corticosteroids such as MEDROL are excreted in breast milk. Corticosteroids such as MEDROL distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants.

Fertility

Corticosteroids including MEDROL have been shown to impair fertility in animal studies.

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 may occur during treatment with MEDROL. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse reactions are listed by system organ class and ranked by frequency where possible.

MedDRA system organ class	**Frequency‡**	**Adverse reactions**
Infections and	Not known	Opportunistic infection,

infestations		infection
Blood and lymphatic system disorders	Not known	Leucocytosis
Immune system disorders	Not known	Medicine hypersensitivity (including anaphylactic reaction and anaphylactoid reaction),
Endocrine disorders	Frequent	Cushingoid
	Not known	Steriod withdrawal syndrome, hypothalamic pituitary adrenal axis suppression
Metabolism and nutrition disorders	Frequent	Sodium retention, fluid retention, diabetes mellitus
	Not known	Metabolic acidosis, alkalosis hypokalaemic, impaired glucose tolerance, increased insulin requirement (or oral hypoglycaemic medicines in diabetics), lipomatosis, increased appetite (which may result in increased weight),
Psychiatric disorders	Not known	Affective disorder

		(including depressed mood and euphoric mood), psychotic disorder (including mania, delusion, hallucination and schizophrenia), affect lability, medicine dependence, suicidal ideation), mental disorder, personality change, confusional state, anxiety, mood swings, insomnia, irritability, abnormal behaviour,
Nervous system disorders	Less frequent	Increased intracranial pressure (with papilloedema [benign intracranial hypertension])
	Not known	Spinal epidural lipomatosis with neurological deficits, paraesthesia, paralysis, , seizure, amnesia, cognitive disorder, dizziness, headache
Eye disorders	Less frequent	Cataract,

	Not known	Glaucoma, exophthalmos, chorioretinopathy with retinal detachment
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Congestive cardiac failure (in susceptible patients)
Vascular disorders	Less frequent	Hypertension
	Not known	Venous thrombosis, hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Hiccups, pulmonary embolism
Gastrointestinal disorders	Less frequent	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage)
	Not known	Intestinal perforation, gastric haemorrhage, pancreatitis, ~~ulcerative~~ oesophagitis ulcerative, oesophagitis, abdominal distention~~,~~ peritonitis, abdominal pain, diarrhoea, dyspepsia, nausea
Skin and subcutaneous	Not known	Skin atrophy, acne,

tissue disorders		angioedema, hirsutism, petechiae, ecchymosis, erythema, hyperhidrosis, skin striae, rash, pruritus, urticaria,
Musculoskeletal and connective tissue disorders	Frequent	Muscular weakness, Osteoporosis, growth retardation
	Less frequent	Osteonecrosis
	Not known	Myalgia, myopathy, muscle atrophy, bone fracture, neuropathic arthropathy, arthralgia
Reproductive system and breast disorders	Not known	Irregular menstruation, amenorrhoea
General disorders and administration site conditions	Frequent	Impaired healing
	Not known	Malaise, fatigue
Investigations	Frequent	Blood potassium decreased
	Not known	Increased urine calcium, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood

		alkaline phosphatase (ALP), increased intraocular pressure, decreased carbohydrate tolerance, Suppression of reactions to skin tests*
Injury, poisoning and procedural complications	Less frequent	Tendon rupture
	Not known	Spinal compression fracture

* Not a MedDRA PT

Post-marketing side effects

MedDRA system organ class	**Adverse reactions**
Infections and infestations	Peritonitis†

† Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids.

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

MEDROL is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.1 Anti-rheumatics (Anti-inflammatory agents)

Methylprednisolone has anti-inflammatory steroid activity. The relative potency of methylprednisolone to hydrocortisone is at least four to one.

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, is secreted in breast milk and across the placenta. Its apparent volume of distribution is approximately 1,4 L/kg. The plasma protein binding of methylprednisolone in humans is approximately 77 %.

Biotransformation

In humans, methylprednisolone is metabolised 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 medicine interactions based on CYP3A4-mediated metabolism, see section 4.5.

Methylprednisolone 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch

Sucrose

Calcium stearate

Mineral oil (Liquid paraffin) (Medrol 16 mg only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Medrol 4 mg blister packs: 36 months

Medrol 16 mg HDPE bottles: 36 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

MEDROL 4 mg: Aluminium/clear PVC foil blister strips of 30 or 100 tablets and/or HDPE bottles containing 30 tablets.

MEDROL 16 mg: HDPE 45 mL bottles containing 50 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REFERENCE NUMBERS

MEDROL 4 mg: C729 (Act 101/1965)

MEDROL 16 mg: C728 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

MEDROL 4 mg: Not applicable – Old medicine

MEDROL 16 mg: Not applicable – Old medicine

10. DATE OF REVISION OF THE TEXT

26 January 2024

BOTSWANA: S2 MEDROL 4 mg: Reg. No.: B9312065 MEDROL 16 mg: Reg. No.: B9312070
NAMIBIA: NS2 MEDROL 4 mg: 14/21.5.1/0436 MEDROL 16 mg: 14/21.5.1/0531