NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MEDROL® 4 mg tablets

MEDROL 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MEDROL 4 mg tablets: Each 4 mg tablet contains 4 mg methylprednisolone.

MEDROL 100 mg tablets: Each 100 mg tablet contains 100 mg methylprednisolone.

Excipients with known effect

MEDROL 4 mg tablets contain:

- lactose monohydrate
- sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MEDROL tablets 4 mg

Tablet: White, flat, elliptical, coded "MEDROL 4" on one side, double scored on the reverse.

The score line is not intended for breaking the tablet.

MEDROL tablets 100 mg

Tablet: Light blue, round, biconvex cross-scored, coded "Upjohn 3379".

The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MEDROL (methylprednisolone) is indicated in the following conditions:

Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance):

- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis
- Hypercalcaemia associated with cancer

Non-Endocrine Disorders

Rheumatic Disorders

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

- Psoriatic arthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Ankylosing spondylitis
- Acute and subacute bursitis
- Acute nonspecific tenosynovitis
- Acute gouty arthritis
- Post-traumatic osteoarthritis
- Synovitis of osteoarthritis
- Epicondylitis

Collagen Diseases

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

- Systemic lupus erythematosus
- Systemic dermatomyositis (polymyositis)
- Polymyalgia rheumatica
- Giant cell arteritis
- Acute rheumatic carditis

Dermatologic Diseases

- Pemphigus
- Bullous dermatitis herpetiformis
- Severe erythema multiforme (Stevens-Johnson syndrome)
- Exfoliative dermatitis
- Mycosis fungoides

- Severe psoriasis
- Severe seborrhoeic dermatitis

Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment:

- Seasonal or perennial allergic rhinitis
- Serum sickness
- Bronchial asthma
- Drug hypersensitivity reactions
- Contact dermatitis
- Atopic dermatitis

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
- Diffuse posterior uveitis and choroiditis
- Sympathetic ophthalmia
- Allergic conjunctivitis
- Keratitis
- Chorioretinitis
- Optic neuritis
- Iritis and iridocyclitis

Respiratory Diseases

- Symptomatic sarcoidosis
- Loeffler's syndrome not manageable by other means
- Berylliosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- Aspiration pneumonitis

Haematologic Disorders

- Idiopathic thrombocytopenia purpura in adults

- Secondary thrombocytopenia in adults
- Acquired (autoimmune) haemolytic anaemia
- Erythroblastopenia (RBC anaemia)
- Congenital (erythroid) hypoplastic anaemia

Neoplastic Diseases

For palliative management of:

- Leukemias and lymphomas in adults
- Acute leukaemia of childhood

Edematous States

To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uraemia, of the idiopathic type or that due to lupus erythematosus.

Gastrointestinal Diseases

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

- Ulcerative colitis
- Regional enteritis

Nervous System

- Acute exacerbations of multiple sclerosis
- Management of oedema associated with brain tumour.

Miscellaneous

- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- Trichinosis with neurologic or myocardial involvement

Organ Transplantations

4.2 Dose and method of administration

Dose

Because complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

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.

The initial dosage of MEDROL Tablets may vary from 4 mg to 48 mg of methylprednisolone per day 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.

Do not halve the tablets.

Clinical situations in which high dose therapy may be indicated include cerebral oedema (200 - 1,000 mg/day), organ transplantation (up to 7 mg/kg/day), and multiple sclerosis. In treatment of acute exacerbations of multiple sclerosis, oral methylprednisolone regimens of 500 mg/day for 5 days or 1000 mg/day for 3 days have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone). 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. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

It should be emphasised that dosage requirements are variable and must be individualised on the basis of the disease under treatment and the response of the patient. After a favourable 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 MEDROL for a period of time consistent with the patient's condition.

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

The rationale for this treatment schedule is based on two major premises:

The anti-inflammatory or therapeutic effect of corticoids persists longer than their physical presence and metabolic effects, and

Administration of the corticosteroid every other morning allows for re-establishment of more nearly normal hypothalamic-pituitary-adrenal (HPA) activity on the off-corticosteroid day.

The following should be kept in mind when considering alternate day therapy:

Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of corticosteroids.

ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacologic corticosteroid therapy is anticipated.

In less severe disease processes in which corticosteroid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states usually will require daily divided high dose therapy for initial control of the disease process. The initial suppressive dose level should be continued until satisfactory clinical response is obtained, usually four to ten days in the case of many allergic and collagen diseases. It is important to keep the period of initial suppressive dose as brief as possible, particularly when subsequent use of alternate day therapy is intended.

Once control has been established, two courses are available:

- Change to ADT and then gradually reduce the amount of corticosteroid given every other day, or
- Following control of the disease process reduce the daily dose of corticosteroid to the lowest effective level as rapidly as possible and then change over to an alternate day schedule. Theoretically, course (i) may be preferable.

Because of the advantages of ADT, it may be desirable to try patients on this form of therapy who have been on daily corticosteroids for long periods of time (eg. patients with rheumatoid arthritis). Since these patients may already have suppressed HPA axis, establishing them on ADT may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over. It may be helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose if difficulty is encountered. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.

As indicated above, certain corticosteroids, because of their prolonged suppressive effect on adrenal activity, are not recommended for alternate day therapy (e.g. dexamethasone and betamethasone).

The maximal activity of the adrenal cortex is between 2.00am and 8.00am, and it is minimal between 4.00pm and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (am).

In using ADT it is important, as in all therapeutic situations, to individualise and tailor the therapy to each patient. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient to understand and tolerate the possible flare-up in symptoms which may occur in the latter part of the off-corticosteroid day. Other symptomatic therapy may be added or increased at this time if needed.

In the event of an acute flare-up of the disease process, it may be necessary to return to a full suppressive daily divided corticosteroid dose for control. Once control is again established alternate day therapy may be reinstituted.

Although many of the undesirable features of corticosteroid therapy can be minimised by ADT, as in any therapeutic situation, the physician must carefully weigh the benefit risk ratio for each patient in whom corticosteroid therapy is being considered.

4.3 Contraindications

MEDROL is contraindicated in patients who have:

- Systemic infections, unless specific anti-infective therapy is given.
- Known hypersensitivity to methylprednisolone or any component of the formulation.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (see section 4.4, Immunosuppressive Effects/Increased Susceptibility to Infections).

4.4 Special warnings and precautions for use

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. Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Immunosuppressive Effects/Increased Susceptibility to Infections

Due to their suppression of the inflammatory response and immune function, corticosteroids may increase susceptibility to fungal, bacterial and viral infections and their severity. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, they should seek urgent medical attention. Passive immunisation is recommended if non-immune patients who come into contact with chicken pox. If a diagnosis of chicken pox is confirmed the illness warrants specialist care and urgent treatment.

The immunosuppressive effects of corticosteroids may also result in activation of latent infection or exacerbation of existing infection. Corticosteroids should be used with great care in patients with known or suspected parasitic infections such as Strongyloides infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicaemia.

It is important to note that corticosteroids may increase susceptibility to infection, may mask some signs of infection, which may reach an advanced stage before the infection is recognised, and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

MEDROL is not recommended for use in patients with septic shock or sepsis syndrome. 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, a systematic review concluded that 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 those with vasopressor-dependent septic shock.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids and should be postponed until at least three months after stopping corticosteroid therapy. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunisation procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

The use of methylprednisolone 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.

Immune System Effects

Allergic reactions (e.g. angioedema) may occur.

Because rare instances of skin reactions and anaphylactic/anaphylactoid reactions (e.g. bronchospasm) 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 (or those who have discontinued treatment but continue to experience symptoms of adrenal insufficiency) who are subjected to unusual stress such as intercurrent illness, trauma or surgery, increased dosage (or reinstitution) of rapidly acting corticosteroids may be required.

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 minimised by use of alternate-day therapy (see section 4.2, Alternate Day Therapy (ADT)).

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Therefore, withdrawal of corticosteroid should always be gradual.

Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

Drug-induced adrenocortical insufficiency may be minimised by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy, therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

A steroid "withdrawal syndrome", seemingly unrelated to adrenocortical insufficiency, may occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

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

Corticosteroids should be used with caution in patients with hypothyroidism as there is potential for an enhanced effect of corticosteroids in these patients.

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.

Metabolism and Nutrition

Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes and predisposes those on long term corticosteroid therapy to diabetes mellitus. Therefore, corticosteroids should be used with caution in patients with diabetes mellitus or a family history of diabetes mellitus.

Psychiatric Effects

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids. Therefore, particular care is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders.

Potentially severe psychiatric adverse reactions may occur with systemic corticosteroids (see section 4.8). 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; 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 systemic steroids.

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 (see section 4.4, Musculoskeletal Effects).

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids 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, typically with long-term use at high doses.

Ocular Effects

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible risk of corneal scarring, loss of vision and corneal perforation.

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

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

Visual Disturbance

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.

Cardiac Effects

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.

Vascular Effects

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.

Corticosteroids should be used with caution in patients with hypertension.

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 non-specific ulcerative colitis if there is a probability of impending perforation, abscess or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, or active or latent peptic ulcer.

Hepatobiliary Effects

Corticosteroids should be used with caution in patients with hepatic failure.

Hepatobiliary disorders have been reported which may be reversible after discontinuation of therapy. Therefore appropriate monitoring is required.

There is an enhanced effect of corticosteroids in patients with cirrhosis.

Musculoskeletal Effects

Corticosteroids should be used with caution in patients with myasthenia gravis who are receiving anticholinesterase therapy as corticosteroid use may decrease plasma anticholinesterase activity.

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 generalised, 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.

Corticosteroids should be used with caution in patients with osteoporosis. Osteoporosis is a common but infrequently recognised adverse effect associated with a long-term use of large doses of glucocorticoid.

Corticosteroid should be used with caution in patients with Duchenne's muscular dystrophy since transient rhabdomyolysis and myoglobinuria have been reported following strenuous activities.

Corticosteroids should be used with caution in patients with previous steroid myopathy.

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.

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.

Discontinuation (see section 4.4, Endocrine Effects)

Injury, Poisoning and Procedural Complications

Systemic corticosteroids are not indicated for, and should therefore not be used to treat traumatic brain injury. A multicentre study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone compared to placebo. A causal association with methylprednisolone treatment has not been established.

Other

Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids (see section 4.5, Other Interactions, *NSAIDs*).

Paediatric Use

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Corticosteroids may cause growth retardation in infancy, childhood and adolescence. The effects may be irreversible, therefore long-term daily-divided doses of corticosteroids should be avoided in these patients.

In infants, children and adolescents, corticosteroid treatment should be administered where possible as a single dose on alternate days for the shortest possible duration.

If prolonged therapy is necessary, growth and development of these patients should be carefully monitored.

Increased intracranial pressure with papilloedema (pseudotumour cerebri) in children has been reported, usually after treatment withdrawal of methylprednisolone. 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 use of corticosteroids, particularly long-term use, in the elderly should be planned bearing in mind the more serious consequences of the common side effects, especially: osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

4.5 Interaction with other medicines and other forms of interaction

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is metabolised mainly 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 compounds are also substrates of CYP3A4, some of which (as well as other medicines) 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, resulting in increased plasma concentration of methylprednisolone. Coadministration of CYP3A4 inhibitors may require titration of methylprednisolone dosage to reduce the risk of adverse effects and avoid steroid toxicity.

CYP3A4 inhibitors include:

- Antifungals such as ketoconazole and itraconazole.
- Antiemetics such as aprepitant and fosaprepitant.
- Immunosuppressants such as ciclosporin. 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 coadministration. Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.
- Macrolide antibacterials such as clarithromycin, erythromycin and troleandomycin.
- HIV-Protease inhibitors such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids. Corticosteroids may induce the metabolism of HIV-protease inhibitors, resulting in reduced plasma concentrations.
- Calcium channel blockers such as diltiazem.
- Isoniazid may increase the plasma concentration of methylprednisolone. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.

- Oral contraceptives such as ethinylestradiol and norethisterone, retard the metabolism of corticosteroids due to increased binding to globulin, resulting in increased plasma levels of corticosteroids and potentiating their biological effect. The dose of corticosteroids may need to be adjusted when commencing or stopping oral contraceptive therapy.
- Grapefruit juice.

CYP3A4 Inducers

Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentrations of methylprednisolone. Coadministration of these substances may require an increase in methylprednisolone dosage to achieve the desired result.

CYP3A4 inducers include:

- Anticonvulsants such as phenobarbital, phenytoin, carbamazepine and primidone.
- Bactericidal antibiotics such as rifampicin and rifabutin.

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 coadministration. Most CYP3A4 inhibitors are also CYP3A4 substrates.

- Immunosuppressants such as cyclophosphamide and tacrolimus.

Other Interactions

Other interactions and effects that occur with methylprednisolone are described below.

Antacids

Concurrent use may decrease absorption of corticosteroids. Efficacy may be reduced sufficiently to require dosage adjustments in patients receiving small doses of corticosteroids.

Antidiabetic Agents

Corticosteroids may increase blood glucose levels. Dose adjustments of antidiabetic therapy may be required with concurrent therapy.

Anticholinergics

Corticosteroids may influence the effect of anticholinergics.

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 Effects).

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.

Anticoagulants (Oral)

The effect of methylprednisolone 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 (such as INR or prothrombin time) should be monitored to maintain the desired anticoagulant effects.

Aromatase Inhibitors

Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

Cardiac Glycosides

There is a risk of toxicity if hypokalaemia occurs due to corticosteroid treatment.

Diuretics and Other Potassium Depleting Agents

Excessive potassium loss maybe experienced with concurrent use of corticosteroids and potassium depleting diuretics (such as frusemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide). 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.

Mifepristone

The effect of corticosteroids may be reduced for 3-4 days after taking mifepristone.

NSAIDs

Concomitant administration may increase the risk of gastrointestinal bleeding and ulceration.

Methylprednisolone may increase the renal 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.

Somatropin

Concomitant administration may inhibit the growth promoting effect of somatropin.

Sympathomimetics

There is an increased risk of hypokalaemia with concurrent high doses of corticosteroids and sympathomimetics such as salbutamol, salmeterol, terbutaline or formoterol.

Vaccines

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Some animal studies have shown that corticosteroids (such as methylprednisolone) have been shown to increase the incidence of fetal malformations of various kinds (cleft palate, skeletal malformations), embryo-fetal lethality (e.g., increase in resorptions), intra-uterine growth retardation and abortion. 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, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

Corticosteroids readily cross the placenta. An increased incidence of low-birth weights in infants born of mothers receiving corticosteroids has been reported. In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid 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, although neonatal adrenal insufficiency is rarely reported in infants exposed *in utero* to corticosteroids.

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

Labour and Delivery

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

Lactation

Corticosteroids are excreted in breast milk.

Corticosteroids distributed into breast milk may suppress growth and 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 adverse effects listed in the table below are typical for all systemic corticosteroids. Their inclusion in this list does not necessarily indicate that the specific event has been observed with Medrol.

The adverse effects for methylprednisolone are listed below by system organ class and frequency.

Infections and Infestations

Not known: Opportunistic infection, infection[a], peritonitis[c], oesophageal candidiasis.

Blood and Lymphatic System Disorders

Not known: Leucocytosis

Immune System Disorders

Not known: Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction.

Endocrine Disorders

Not known: Cushingoid, hypopituitarism, steroid withdrawal syndrome.

Metabolism and Nutrition Disorders

Not known: Metabolic acidosis, sodium retention, fluid retention, alkalosis hypokalaemic, dyslipidaemia, glucose tolerance impaired[b], increased insulin requirement (or oral hypoglycaemic agents in diabetics), lipomatosis, increased appetite (which may result in weight increased).

Psychiatric Disorders

Not known: Affective disorder (including depressed mood, euphoric mood, affect lability, drug dependence, suicidal ideation), psychotic disorder (including mania, delusion, hallucination and schizophrenia), psychotic behaviour, mental disorder, personality change, confusional state, anxiety, mood swings, abnormal behaviour, insomnia, irritability.

Nervous System Disorders

Not known: Epidural lipomatosis, intracranial pressure increased (with papilloedema [benign intracranial hypertension]), seizure, amnesia, cognitive disorder, dizziness, headache.

Eye Disorders

Uncommon: Vision, blurred (see also section 4.4).

Not known: Chorioretinopathy, cataract, glaucoma, exophthalmos, corneal thinning, 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: Thrombosis, hypertension, hypotension.

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), intestinal perforation, gastric haemorrhage, pancreatitis, oesophagitis ulcerative, oesophagitis, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea.

Skin and Subcutaneous Tissue Disorders

Not known: Angioedema, hirsutism, petechiae, ecchymosis, skin atrophy, erythema, hyperhidrosis, skin striae, rash, pruritus, urticaria, acne, telangiectasia.

Musculoskeletal and Connective Tissue Disorders

Not known: Muscular weakness, myalgia, myopathy, muscle atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, growth retardation.

Reproductive System and Breast Disorders

Not known: Menstruation irregular, amenorrhoea.

General Disorders and Administration Site Conditions

Not known: Impaired healing, oedema peripheral, fatigue, malaise.

Investigations

Not known: Intraocular pressure increased, carbohydrate tolerance decreased, blood potassium decreased, calcium balance negative, urine calcium increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, suppression of reactions to skin tests[d].

Injury, Poisoning and Procedural Complications

Not known: Spinal compression fracture, tendon rupture.

[a] Including increased susceptibility to and severity of infections, masking of infections and latent infections (e.g. tuberculosis) becoming active.
[b] Manifestations of latent diabetes mellitus.
[c] Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (see section 4.4).

[d] Not a MedDRA preferred term.

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. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids. 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Methylprednisolone is a potent anti-inflammatory steroid. It has greater anti-inflammatory potency than prednisolone, even less tendency than prednisolone to induce sodium and water retention. 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.

The mean oral time of peak concentration is 1.1 - 2.2 hours.

Distribution

Methylprednisolone is widely distributed throughout the body and is described by a two-compartment model. The mean volume of distribution reported in 34 adult volunteers ranged from 41 to 61.5 L.

Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, the placental 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%.

MEDROL readily crosses the blood-brain barrier into the central nervous system with peak CSF levels being 5 - 6% of the corresponding plasma levels. Methylprednisolone peak CSF levels occurred within five minutes to one hour after IV administration of a 500mg dose to patients with lupus cerebritis.

Biotransformation

In humans, methylprednisolone is metabolised in the liver to inactive metabolites, the major ones 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.

Following IV administration of radiolabelled 6-methylprednisolone to six cancer patients, 75% of total reactivity was recovered in the urine after 96 hours and 9% in the faeces after five days. Twenty percent of the total dose was excreted in the bile, but the time course was not cited.

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

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.

Effects on Fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MEDROL 4 mg tablet

Calcium stearate

Lactose monohydrate

Maize starch

Purified water

Sucrose

MEDROL 100 mg tablet

Microcrystalline cellulose

Sodium starch glycollate

FD&C blue N°2 Aluminium lake

Methylcellulose

Magnesium stearate

6.2 Incompatibilities

None stated.

6.3 Shelf life

MEDROL 4 mg tablets, bottle: 18 months

MEDROL 4 mg tablets, blister pack: 60 months

MEDROL 100 mg tablets, bottle: 60 months

6.4. Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

MEDROL tablets 4 mg are available in HDPE bottles of 100. The PVC blister packs of 100 tablets are registered but not distributed in New Zealand.

MEDROL tablets 100 mg are available in glass bottles of 20.

6.6 Special precautions for disposal and other handling

Do not halve tablets.

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Ltd.

P O Box 3998

Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

Medrol 4 mg tablets – 31 December 1969

Medrol 100 mg tablets – 07 August 1987

10. DATE OF REVISION OF THE TEXT

3 December 2019

® Medrol is a registered trademark of Pfizer Inc.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Revise dosing recommendation for acute exacerbations of multiple sclerosis.