SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

MEDROL™ 4 mg Tablets

MEDROL™ 16 mg Tablets

COMPOSITION:

Each 4 mg tablet contains 4 mg methylprednisolone

Each 16 mg tablet contains 16 mg methylprednisolone

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 Anti-rheumatics (Anti-inflammatory agents)

PHARMACOLOGICAL ACTION:

Naturally occurring glucocorticoids (hydrocortisone and cortisone) which also have salt retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogues are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

INDICATIONS:

1. **Endocrine Disorders:**

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

   Congenital adrenal hyperplasia

   Hypercalcemia associated with cancer

   Nonsuppurative thyroiditis

2. **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

3. **Collagen Diseases**:

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

Systemic lupus erythematosus

Acute rheumatic carditis

4. **Dermatological Diseases:**

Pemphigus

Exfoliative dermatitis

Bullous dermatitis herpetiformis

Mycosis fungoides

Severe erythema multiforme

Severe psoriasis

5. **Allergic Conditions:**

Control of severe or incapacitating allergic conditions intractable to adequate treatment with conventional drugs.

Seasonal or perennial allergic rhinitis

Serum sickness

Bronchial Asthma

Angioedema

Contact dermatitis

Urticaria

Atopic dermatitis

6. **Ophthalmic Diseases:**

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

Allergic corneal marginal ulcers

Allergic conjunctivitis

Herpes zoster ophthalmicus

Keratitis

Anterior segment inflammation

Chorioretinitis

Diffuse posterior uveitis and choroiditis

Sympathetic ophthalmia

Iritis and iridocyclitis

Optical neuritis

7. **Respiratory Diseases:**

Symptomatic sarcoidosis

Loeffler's syndrome not manageable by other means

Berylliosis

Pulmonary emphysema where bronchospasm or bronchial edema plays a significant role

Fulminating or disseminated pulmonary tuberculosis when concurrently accompanied by appropriate anti-tuberculosis therapy

Diffuse interstitial pulmonary fibrosis (Hamman Rich syndrome)

8. **Haematological Disorders:**

Idiopathic and secondary thrombocytopeniain adults

Acquired (autoimmune) haemolytic anaemia

Erythroblastopenia (RBC anaemia)

Congenital (erythroid) hypoplastic anaemia

9. **Neoplastic Diseases:**

For palliative management of:

Leukaemias and lymphomas in adults

Acute leukaemia of childhood

10. **Edematous 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 agents, in:

Cirrhosis of the liver with refractory ascites

Refractory congestive heart failure

11. **Gastro-intestinal Diseases:**

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

Ulcerative colitis

Intractable sprue

Regional enteritis

12. **Miscellaneous:**

Tuberculous meningitis with subarachnoid block or impending block when concurrently accompanied by appropriate antituberculous chemotherapy

Dental postoperative inflammatory reactions

Systemic dermatomyositis (polymyositis)

CONTRA-INDICATIONS:

Systemic fungal infections.

WARNINGS:

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of the possible hazards of neurological complications and a lack of antibody response.

DOSAGE AND DIRECTIONS FOR USE:

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 EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED 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 drug 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 drug 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 drug 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 drug 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 corticoid 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 corticoids while minimizing certain undesirable effects, including pituitary-adrenal suppression, the cushingoid state, corticoid withdrawal symptoms and growth suppression in children.

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

(a) The anti-inflammatory or therapeutic effects of corticoids persist longer than their physical presence and metabolic effect, and;

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

A brief review of the HPA physiology may be helpful in understanding this rationale. Acting primarily through the hypothalamus, a fall in free cortisol stimulates the pituitary gland to produce increasing amounts of corticotropin (ACTH) while a rise in free cortisol inhibits ACTH secretion. Normally the HPA system is characterized by diurnal (circadian) rhythm. Serum levels of ACTH rise from a low point at about 10 p.m. to a peak level at about 6 a.m. Increasing levels of ACTH stimulate adrenal cortical activity resulting in a rise in plasma cortisol with maximal levels occurring between 2 a.m. and 8 a.m. This rise in cortisol dampens ACTH production and in turn, adrenal cortical activity. There is a gradual fall in plasma corticoids during the day with lowest levels occurring at about midnight.

The diurnal rhythm of the HPA axis is lost in Cushing's disease, a syndrome of adrenal cortical hyper-function characterized by obesity with centripetal fat distribution, thinning of the skin with easy bruisability, muscle wasting with weakness, hypertension, latent diabetes, osteoporosis, electrolyte imbalance, etc. The same clinical findings of hyperadrenocorticism may be noted during long-term pharmacological doses of corticoid therapy administered in conventional daily divided doses. It would appear then, that a disturbance in the diurnal cycle with maintenance of elevated corticoid values during the night may play a significant role in the development of undesirable corticoid effects. Escape from these constantly elevated plasma levels for even short periods of time may be instrumental in protecting against undesirable pharmacological effects.

During conventional therapy using pharmacological doses of corticosteroids, ACTH production is inhibited with subsequent suppression of cortisol production by the adrenal cortex.

Recovery time for normal HPA activity is variable depending upon the dose and duration of treatment. During this time the patient is vulnerable to any stressful situation. Although it has been shown that there is considerably less adrenal suppression following a single morning dose of prednisolone (10 mg) as opposed to a quarter of that dose administered every 6 hours, there is evidence that some suppressive effect on adrenal activity may be carried over into the following day when pharmacologic doses are used. Further, it has been shown that a single dose of certain corticosteroids will produce adrenal cortical suppression for two or more days. Other corticoids, including methylprednisolone, hydrocortisone, prednisone, and prednisolone, are considered to be short acting (producing adrenal cortical suppression for 1¼ to 1½ days following a single dose) and thus are recommended for alternate day therapy.

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

(1) Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of steroids.

(2) ADT is a therapeutic technique primarily designed for patients in whom long-term pharmacological corticoid therapy is anticipated.

(3) In less severe disease processes in which corticoid therapy is indicated, it may be possible to initiate treatment with ADT. More severe disease states will usually 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 dosage as brief as possible particularly when subsequent use of alternate-day therapy is intended.
Once control has been established, two courses are available:

(a) change to ADT and then gradually reduce the amount of corticoid given every other day, or;

(b) following control of the disease process reduce the daily dose of corticoid to the lowest effective level as rapidly as possible and then change over to an alternate-day schedule.

Theoretically, course (a) may be preferable.

(4) Because of the advantages of ADT, it may be desirable to try patients who have been on daily corticoids for long periods of time, on this form of therapy (e.g. patients with rheumatoid arthritis). Since these patients may already have a 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.

(5) 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).

(6) The maximal activity of the adrenal cortex is between 2 a.m. and 8 a.m. and it is minimal between 4 p.m. and midnight. Exogenous corticosteroids suppress adrenocortical activity the least when given at the time of maximal activity (a.m.).

(7) In using ADT it is important as in all therapeutic situations to individualize 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-steroid day. Other symptomatic therapy may be added or increased at this time if needed.

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

(9) 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 corticoid therapy is being considered.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Fluid and Electrolyte Disturbances:

Sodium retention

Potassium loss

Fluid retention

Hypokalemic alkalosis

Congestive heart failure in susceptible patients

Hypertension

Musculoskeletal:

Muscle weakness

Vertebral compression fractures

Steroid myopathy

Aseptic necrosis of femoral and hymeral heads

Loss of muscle mass

Pathological fracture of long bones

Osteoporosis

Gastro-intestinal:

Peptic ulcer with possible perforation and haemorrhage

Abdominal distension

Ulcerative esophagitis

Pancreatitis

Dermatological:

Impaired wound healing

Facial erythema

Thin fragile skin

Increased sweating

Petechiae and ecchymoses

May suppress reactions to skin tests

Neurological:

Increased intracranial pressure with papilloedema pseudo-tumour cerebri usually after treatment

Convulsions

Vertigo

Headache

Endocrine:

Development of cushingoid state

Menstrual irregularities

Suppression of growth and pituitary hormone in children

Decreased carbohydrate tolerance: manifestations of latent diabetes mellitus, Increased requirements for insulin or oral hypoglycaemic agents

Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness

Ophthalmic:

Posterior subcapsular cataracts

Glaucoma

Increased intraocular pressure

Exophthalmos

Metabolic:

Negative nitrogen balance due to protein catabolism

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

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

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

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.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestation. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Corticoteroids 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, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis or myasthenia gravis.

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

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

Corticosteroids may mask some signs of infection and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts or glaucoma, with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Usage in pregnancy:
Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, lactating mothers or women of childbearing age requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or foetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

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.

The use of MEDROL 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 anti-tuberculosis 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Treatment should be symptomatic and supportive.

IDENTIFICATION:

MEDROL 4 mg tablet - a white, elliptical tablet, cross-scored on one side and marked with "Upjohn" on the other side.

MEDROL 16 mg tablet - a white, elliptical tablet, cross-scored on one side and marked with "Medrol 16" on the other side.

PRESENTATION:

MEDROL 4 mg - blister packs of 30 and 100 tablets.

MEDROL 16 mg - bottles of 50 tablets.

STORAGE INSTRUCTIONS:

Store at room temperature (15 ºC - 30 °C).

Keep out of reach of children.

REFERENCE NUMBERS:

Medrol 4 mg - C729 (Act 101/1965)

Medrol 16 mg - C728 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Pfizer Laboratories (Pty) Ltd

85 Butelane

Sandton

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South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

5 January 1982

BOTSWANA: S2

Medrol 4mg Reg no. B9312065

Medrol 16mg Reg no. B9312070

NAMIBIA: S2

Medrol 4mg Reg no.14/21.5.1/0436

Medrol 16mg Reg no.14/21.5.1/0531