METHYLPREDNISOLONE

METCORT®

4 mg and 16 mg TABLET

Corticosteroid

FORMULATION
Each tablet contains:
Methylprednisolone …….. 4 mg or 16 mg

PRODUCT DESCRIPTION
Methylprednisolone 4 mg Tablet is a white to off-white, standard concave round tablet, bisected on one side and plain on the other side.
Methylprednisolone 16 mg Tablet is a white to off-white, square tablet, plain on both sides.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Methylprednisolone is a synthetic glucocorticoid and a methyl derivative of prednisolone. It is a moderately potent glucocorticoid with only slight mineralocorticoid activity.Methylprednisolone is a potent anti-inflammatory agent with the capacity to profoundly inhibit the immune system. Methylprednisolone 4 mg is equivalent to about 5 mg of prednisolone in terms of anti-inflammatory activity. In addition, methylprednisolone has a lesser tendency to induce sodium and water retention compared with prednisolone.

Pharmacokinetics
The pharmacokinetics of methylprednisolone is linear, independent of the route of administration.

After oral administration, methylprednisolone achieves its maximum plasma concentration in about 1.5 to 2.3 hours across doses in healthy adults. Mean oral time to peak concentration is achieved in about 1.1 to 2.2 hours. The oral bioavailability of methylprednisolone is 82 to 89%.

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

Similar to many CYP3A4 substrates, methylprednisolone may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein which may influence tissue distribution and interactions with other medicines.

Methylprednisolone is widely distributed into tissues and is bound to plasma protein (approximately 77%). It crosses the blood-brain barrier into the central nervous system with peak CSF levels being 5% to 6% of the corresponding plasma levels. It also crosses the placenta and is secreted in breastmilk.

Methylprednisolone is extensively metabolized in the liver to inactive metabolites, mainly 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Metabolism in the liver occurs primarily via the CYP3A4 enzyme.

The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours.

Radiolabeled 6-methylprednisolone was administered intravenously to six cancer patients. Seventy-five percent (75%) of total radioactivity was recovered in the urine after 96 hours and 9% in the feces after five days. Twenty percent (20%) of the total dose was excreted in the bile; however, the time course was not cited.

INDICATIONS

Endocrine Disorders
• Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs like dexamethasone may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance) • Congenital adrenal hyperplasia • Nonsuppurative thyroiditis • Hypercalcemia associated with cancer
Rheumatic Disorders
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in: • Post-traumatic osteoarthritis • Synovitis of osteoarthritis • 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 • Psoriatic arthritis • Epicondylitis
Collagen Diseases
During an exacerbation or as maintenance therapy in selected cases of: • Systemic lupus erythematosus • Polymyalgia rheumatica • Systemic dermatomyositis (polymyositis) • Giant cell arteritis • Acute rheumatic carditis
Dermatologic Diseases
• Pemphigus vulgaris • Severe erythema multiforme (Stevens-Johnson syndrome) • Bullous dermatitis herpetiformis • Exfoliative dermatitis • Mycosis fungoides • Severe seborrheic dermatitis • Severe psoriasis
Allergic States
Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment: • Bronchial asthma • Seasonal or perennial allergic rhinitis • Allergic contact dermatitis • Atopic dermatitis • Serum sickness • Drug hypersensitivity reactions
Ophthalmic Diseases
Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa, such as: • Herpes zoster ophthalmicus • Anterior uveitis (iritis, iridocyclitis) • Diffuse posterior uveitis and choroiditis • Chorioretinitis • Optic neuritis • Sympathetic ophthalmia • Anterior segment inflammation • Allergic conjunctivitis • Keratitis • Allergic corneal marginal ulcers
Gastrointestinal Diseases
To tide the patient over a critical period of the disease in: • Ulcerative colitis • Regional enteritis • Crohn's disease
Respiratory Diseases
• Symptomatic sarcoidosis • Berylliosis • Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy • Loeffler's syndrome not manageable by other means • Aspiration pneumonitis
Hematologic Disorders
• Idiopathic thrombocytopenic purpura in adults • Erythroblastopenia (RBC anemia) • Secondary thrombocytopenia in adults • Acquired (autoimmune) hemolytic anemia • Congenital (erythroid) hypoplastic anemia
Neoplastic Diseases
For palliative management of: • Leukemias and lymphomas in adults • Acute leukemia in children
Edematous States
To induce diuresis or remission of proteinuria in nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
Nervous System Disorders
• Acute exacerbations of multiple sclerosis • Management of edema associated with brain tumor
Organ Transplantations
Other Uses
• Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy • Trichinosis with neurologic or myocardial involvement

DOSAGE AND ADMINISTRATION
Complications of corticosteroid treatment are highly variable between patients as are durations of treatment. Dose, duration and mode (daily or intermittent) of treatment should be individually determined based on assessment of risk/benefit.

The lowest effective corticosteroid dose should be used to control the condition being treated. Gradual reduction of dosage is recommended whenever possible.

Dosage should be individualized based on the condition being treated and the patient's response. Maintain and/or adjust initial dosage until a satisfactory response is noted. Discontinue methylprednisolone and shift the patient to other appropriate therapy if clinical response is unsatisfactory after a reasonable period of time. Constant monitoring is needed as regard to dosage. Situations which make dosage adjustments necessary include:

- Changes in clinical status secondary to remissions or exacerbations in the disease process
- The patient's individual drug responsiveness
- The effect of patient exposure to stressful situations not directly related to the disease entity under treatment; it may be necessary to increase the dosage of methylprednisolone for a period of time consistent with the patient's condition.

Recommended Dose:

- ***Usual Initial Dose:*** 4 mg to 48 mg per day given in 4 divided doses depending on the specific disease being treated. However, initial doses of up to 100 mg or more may be used in acute severe disease.
- The initial suppressive dose level may vary depending on the condition being treated. This is continued until a satisfactory clinical response is obtained, a period usually of three to seven days in the case of rheumatic disease (except for acute rheumatic carditis), allergic conditions affecting the skin or respiratory tract and ophthalmic diseases. Re-evaluate the case to confirm the original diagnosis if a satisfactory response is not achieved in seven days. Upon obtaining a satisfactory response, decrease dose in small increments (not more than 2 mg at intervals of 7 to 10 days are suggested) either to terminate treatment in the case of acute conditions (i.e., seasonal asthma, exfoliative dermatitis, acute ocular inflammations) or until the lowest level that maintains an adequate clinical response is reached in chronic conditions (i.e., rheumatoid arthritis, systemic lupus erythematosus, bronchial asthma, atopic dermatitis).
- Clinical situations which may require high dose therapy of corticosteroids such as multiple sclerosis, cerebral edema, and organ transplantation should maintain initial dosage or adjust until a satisfactory response is observed in the patient. Discontinue methylprednisolone and shift the patient to other appropriate therapy if clinical response is unsatisfactory after a reasonable period of time. If there is a lack of satisfactory clinical response after a reasonable period of time, discontinue methylprednisolone and transfer patient to other appropriate therapy. If after long-term therapy the drug is to be stopped, it is recommended that methylprednisolone be discontinued gradually rather than abruptly**.**

Suggested Initial Daily Methylprednisolone Dose
(given either as single dose or in divided doses)

Indications	Recommended Initial Daily Dose
Rheumatoid arthritis	
• Severe	12 to 16 mg
• Moderately severe	8 to 12 mg
• Moderate	4 to 8 mg
• Children	4 to 8 mg
Systemic dermatomyositis	48 mg
Systemic lupus erythematosus	20 to 100 mg
Acute rheumatic fever	48 mg until ESR normal for one week
Allergic diseases	12 to 40 mg
Bronchial asthma	Up to 64 mg single dose/alternate day up to 100 mg maximum
Ophthalmic diseases	12 to 40 mg
Hematological disorders and leukemias	16 to 100 mg
Malignant lymphoma	16 to 100 mg
Ulcerative colitis	16 to 60 mg
Crohn's disease	Up to 48 mg per day in acute episodes
Organ transplantation	Up to 3.6 mg/kg/day
Pulmonary sarcoid	32 to 42 mg on alternate days
Giant cell arteritis/polymyalgia rheumatica	64 mg
Pemphigus vulgaris	80 to 360 mg
Multiple sclerosis	200 mg/day
Cerebral edema	200 to 1000 mg/day

Treatment of Acute Exacerbations of Multiple Sclerosis: 200 mg per day of prednisolone for one week followed by 80 mg every other day for one month have been shown to be effective (4 mg of methylprednisolone is equivalent to 5 mg of prednisolone).

Renal Insufficiency: There is no dosing adjustment recommended in patients with renal insufficiency**.**

Use in Elderly Patients: Methylprednisolone should be used with caution in the elderly especially in the long-term since the incidence of corticosteroid-induced side effects may be increased since these patients have a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy**.**

Use in Pediatric Patients: Methylprednisolone treatment should be based on severity of the condition and response of the patient more than by age, body weight or body surface area. Dosage should be decreased in small decrements to the lowest level that maintains an adequate clinical response after a satisfactory response is obtained. The range of initial doses is 0.117 to 1.66 mg/kg/day (3.3 to 50 mg/m^2 body surface area/day) given in three or four divided doses.

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 rationale of this dosing regimen is for patients requiring long-term pharmacologic dose treatment to receive the beneficial effects of glucocorticoids while minimizing certain undesirable effects (e.g., pituitary-adrenal suppression, Cushingoid state, glucocorticoid withdrawal symptoms, growth suppression in children). This rationale is based on two major premises: the anti-inflammatory or therapeutic effect of glucocorticoids 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**.**

When considering ADT, the following should be kept in mind:

- Basic principles and indications for corticosteroid therapy should apply. The benefits of ADT should not encourage the indiscriminate use of corticosteroids.
- This is usually recommended in patients who require long-term pharmacologic dose corticosteroid treatment.
- It may be possible to initiate treatment with ADT in less severe cases in which corticosteroid therapy is indicated. More severe disease states will usually require daily divided high dose therapy for initial control of the disease. 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 ADT is intended. Once control has been established, either of these two regimens maybe utilized:
  - 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 ADT. Theoretically, the former regimen may be preferable.
- Patients who have been on daily corticosteroids for long periods of time (e.g., patients with rheumatoid arthritis) may already have suppressed HPA axis and establishing them on ADT may be difficult and not always successful. However, it is recommended that regular attempts be made to change them over to ADT. It may helpful to triple or even quadruple the daily maintenance dose and administer this every other day rather than just doubling the daily dose. Once the patient is again controlled, an attempt should be made to reduce this dose to a minimum.
- Certain corticosteroids (e.g., dexamethasone and betamethasone) are not recommended for ADT because of their prolonged suppressive effect on adrenal activity**.**

The maximal activity of the adrenal cortex is between 2:00 a.m. and 8:00 a.m. and it is minimal between 4:00 p.m. and midnight. Exogenous corticosteroids suppress adrenocortical activity the least, when given at the time of maximal activity (a.m.)

It is important to individualize and tailor the therapy to each patient when using ADT. Complete control of symptoms will not be possible in all patients. An explanation of the benefits of ADT will help the patient 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.

It may be necessary to return to a full suppressive daily divided corticosteroid dose for control in the event of an acute flare-up. ADT may be reinstituted once control is re-established.

Although many of the undesirable effect of corticosteroids may be minimized by ADT, the physician must carefully weigh the benefit risk ratio for each patient in whom corticosteroid therapy is considered.

CONTRAINDICATIONS
- Hypersensitivity to methylprednisolone or to any component of the product
- Systemic infections, unless specific anti-infective therapy is given
- Systemic fungal infections
- Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids

WARNINGS AND PRECAUTIONS
Immunosuppressive Effects / Increased Susceptibility to Infections

Glucocorticoids(especially in large doses) suppress the inflammatory response and immune function and may increase susceptibility to and/or mask symptoms of infection (viral, bacterial and fungal). It is not known how the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known.

Corticosteroids may cause decreased resistance and inability to localize infection. Infections caused by any pathogen including viral, bacterial, fungal, protozoan, or helminthic infections in any location of the body may be associated with corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe (at times fatal) and occur more frequently with increasing doses of corticosteroids.

- ***Viral Infections:*** Viral infections such as chicken pox or measles can be more serious or even fatal in non-immunized children or adults on corticosteroids. Patients who have not had these diseases, should take particular care to avoid exposure. Prophylaxis with varicella zoster immune globulin (VZIG) may be indicated if exposed to chicken pox (given within 10 days upon exposure), while prophylaxis with immunoglobulin (IG) may be indicated if exposed to measles. If a diagnosis of chicken pox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.
- ***Special Pathogens:*** Corticosteroids may cause activation of latent diseases or exacerbation of intercurrent infections.

  In patients with known or suspected Strongyloides (threadworm) infestation, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration which is often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia. Use corticosteroids with great care in these patients.
- ***Tuberculosis:*** Use methylprednisolone in active tuberculosis only in fulminating or disseminated cases in which corticosteroids are used with appropriate antituberculous regimen.

  Since reactivity to the disease may occur in patients with latent tuberculosis or tuberculin reactivity, observe these patients closely and administer chemoprophylaxis during prolonged corticosteroid therapy.

The role of corticosteroids in septic shock has been controversial with early studies reporting both beneficial and detrimental effects. Recent studies have shown that supplemental corticosteroids have been beneficial in patients with established septic shock who exhibit adrenal insufficiency. The routine use in septic shock however, is not recommended. A systematic review of short-course high-dose corticosteroids did not support their use. However, a meta-analyses, and a review have suggested that longer courses (5 to 11 days) of low dose corticosteroids may reduce mortality especially in those with vasopressor-dependent septic shock.

Kaposi's sarcoma has been reported in patients receiving corticosteroids. Clinical improvement may be observed upon discontinuation of corticosteroids.

Vaccination
Do not administer live or live attenuated vaccines (including small pox vaccine) in patients receiving corticosteroids. This should be postponed until at least three (3) months after stopping corticosteroid therapy. Although killed or inactivated vaccines may be administered in patients on corticosteroids, response to such vaccines cannot be predicted. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

Hypersensitivity Reactions
Allergic reactions such as angioedema may occur.

Anaphylactoid reactions (e.g., bronchospasm) have occurred rarely in patients receiving parenteral corticosteroid therapy. Prior to methylprednisolone administration, appropriate precautionary measures should be taken especially when the patient has a history of allergy to any drug.

Endocrine Effects
Pharmacologic dose of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnea, anorexia, nausea and vomiting, fever, hypoglycemia, hypotension, and dehydration. This effect is variable among patients and is dependent on dose and duration of treatment and may be minimized by the use of ADT.

In some cases, withdrawal symptoms may stimulate a clinical relapse of the disease for which the patient has been under treatment and therefore clinical assessment of disease activity may be important. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty of HPA suppression, the dose of systemic corticosteroids ***may*** be reduced rapidly to physiologic doses. Dose reduction should be slower once a daily dose of 6 mg methylprednisolone is reached to allow the HPA-axis to recover.

Acute adrenal insufficiency leading to a fatal outcome may also occur if corticosteroids are abruptly withdrawn. Although abrupt withdrawal of doses up to 32 mg/day methylprednisolone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in majority of patients, consider gradual withdrawal of systemic corticosteroid therapy in the following patient groups even after courses lasting 3 weeks or less:

- Those who have had repeated courses of systemic corticosteroids, particularly if taken for > 3 weeks.
- When a short course has been prescribed within one year of discontinuation of long-term therapy (months or years)
- Those who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy. Moreover, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly
- Those receiving systemic corticosteroid doses of >32 mg daily of methylprednisolone
- Those taking doses in the evening repeatedly

Metabolic clearance of corticosteroids may be altered in hypothyroid (decreased clearance) or hyperthyroid (increased clearance) patients. Patient monitoring based on thyroid status may be necessary for these patients.

Glucocorticoids should be avoided in patients with Cushing's disease since the drug can produce or aggravate Cushing's syndrome.

Cardiovascular-Renal Effects
Use corticosteroids with caution, and only if strictly necessary, in cases of congestive heart failure.

Particular care with frequent monitoring is required when considering the use of systemic corticosteroids in the following patients:

- Patients who have experienced a recent myocardial infarction (myocardial rupture has been reported)
- Patients with hypertension
- Patients predisposed to thrombophlebitis
- Patients with renal insufficiency

Sodium retention resulting in edema, potassium loss, hypokalemic alkalosis, and hypertension may occur in patients receiving glucocorticoids. Congestive heart failure may occur in susceptible patients. These effects may occur when synthetic corticosteroids are used in high dosage for prolonged periods. Dietary salt restriction and potassium supplementation may be advised when necessary. All corticosteroids increase calcium excretion which may result in hypocalcemia.

Metabolism and Nutrition Disorders
Use with caution in patients with, or a family history of diabetes mellitus since corticosteroids may cause an increase in blood glucose (steroid-induced diabetes), worsen pre-existing diabetes and predispose those on long-term corticosteroid therapy to diabetes.

Gastrointestinal Effects
An increased risk of perforation has been shown in active or latent peptic ulcers, diverticulitis, abscess or other pyogenic infections, fresh intestinal anastomoses, and nonspecific ulcerative colitis and therefore caution in the use of steroids is recommended.

Hepatobiliary Effects
The effect of corticosteroids is enhanced in patients with cirrhosis. Particular care and frequent monitoring may be required when considering the use of systemic corticosteroids in patients with liver failure or cirrhosis.

Musculoskeletal Effects
Acute myopathy which occurs most frequently in patients with disorders of neuromuscular transmission such as myasthenia gravis, or in patients receiving therapy with neuromuscular blocking agents such as pancuronium, has been observed with use of high doses of corticosteroids. Acute myopathy, which may result in quadriparesis, is generalized and may involve ocular and respiratory muscles. Elevation of creatine kinase may also be observed. Clinical improvement or recovery after stopping corticosteroid therapy may need weeks to years.

Since postmenopausal women and geriatric or debilitated patients are especially prone to osteoporosis, special consideration must be given to these patients prior to initiation of corticosteroid therapy. Frequent patient monitoring is necessary.

Use corticosteroids with caution in patients with Duchenne's muscular dystrophy. Rhabdomyolysis and myoglobinuria have been reported after these patients have engaged in strenuous activity.

Patients with previous steroid myopathy must also use corticosteroids with caution.

Ophthalmic Effects
Prolonged use of corticosteroids may cause posterior subcapsular and nuclear cataracts (particularly in children), exophthalmos or increased intraocular pressure which may result in glaucoma or may occasionally damage the optic nerve. Development of secondary fungal and viral infections of the eye may be enhanced in patients receiving corticosteroids.

Use corticosteroids with caution in active ocular herpes simplex to avoid corneal scarring, loss of vision and corneal perforation.

Neuro-Psychiatric Effects
Corticosteroids should be used with caution in patients with seizure disorders or those with myasthenia gravis.

Although corticosteroids have been shown to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, data do not show that corticosteroids affect the ultimate outcome or natural history of the disease. Relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

Corticosteroids may lead to mental disturbances including euphoria, insomnia, mood swings, anxiety, personality changes, and depression to frank psychoses. Corticosteroids may also aggravate emotional instability or psychotic tendencies. Particular care is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders. Symptoms of potentially severe psychiatric adverse reactions associated with corticosteroid use typically emerge within a few days or weeks of starting treatment. Psychological effects have also been reported upon corticosteroid withdrawal; frequency is unknown.

Injury
High doses of systemic corticosteroids should not be used for the treatment of traumatic brain injury.

Ability to Drive or Use/Operate Machinery
The effect of corticosteroids on the ability to drive or use machinery has not been established. There is no evidence to suggest that methylprednisolone may affect the ability to drive and use machines. No deleterious effect of corticosteroids on driving and operating machinery ability is expected.

INTERACTION WITH OTHER MEDICAMENTS
CYP 3A4 inducers such as barbiturates, phenytoin, primidone, rifampicin, rifabutin, aminoglutethamide, carbamazepine, and other drugs that stimulate hepatic metabolism: These drugs may enhance methylprednisolone metabolism, shorten its plasma half-life and lead to decreased plasma concentrations of methylprednisolone. Increased methylprednisolone dosage may be required.

CYP 3A4 inhibitors such as antifungals (itraconazole, ketoconazole), antiemetics (aprepitant, fosaprepitant), immunosuppressants (ciclosporin, cyclophosphamide, tacrolimus), macrolide antibiotics (clarithromycin, erythromycin, troleandomycin), HIV-protease inhibitors, diltiazem, grapefruit juice: These may decrease methylprednisolone metabolism thereby increasing plasma concentrations of corticosteroids.

Increased activity of both ciclosporin and corticosteroids may occur when the two are used concomitantly. Convulsions have been reported with concomitant use.

Ketoconazole decreases the metabolism of certain corticosteroids by up to 60% leading to an increased risk of corticosteroid side effects.

CYP3A4 substrates such as calcium antagonists (mibefradil), histamine$_1$-receptor antagonists (cimetidine), contraceptives (ethinylestradiol/norethindrone), and calcium channel blockers (nifedipine, felodipine): The hepatic clearance of methylprednisolone may be inhibited or induced in the presence of another CYP3A4 substrate. It is possible that the adverse events associated with the use of either drug alone may be more likely to occur when used concomitantly.

Sympathomimetics (e.g., salbutamol, salmeterol, terbutaline, formoterol): Coadministration with high doses of corticosteroids may result in an increased risk of hypokalemia.

Antivirals: Protease inhibitors (i.e., indinavir and ritonavir) may increase plasma concentrations of corticosteroids. On the other hand, corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.

Antacids: Antacids may decrease the absorption of corticosteroids when given concomitantly. Dose adjustments may be required in patients receiving small doses of corticosteroids.

Oral contraceptives and estrogen: These can cause alterations in plasma protein binding and metabolism of corticosteroids which can result in exposure of women to increased levels of the unbound corticosteroid for long periods of time. Dose adjustments may be warranted when commencing or stopping oral contraceptive therapy. There have also been isolated reports of contraceptive failure in women receiving corticosteroid therapy.

Aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs): Concomitant use results in increased risk of gastrointestinal adverse effects such as gastrointestinal bleeding and ulceration.

Use aspirin cautiously in conjunction with corticosteroids. The clearance of salicylates may be increased with concomitant use which could lead to increased salicylate toxicity when methylprednisolone is withdrawn.

Oral Anticoagulants (warfarin): There is conflicting data on the effect of methylprednisolone and anticoagulants. There are reports of enhanced as well as diminished effects of anticoagulants when given concomitantly. Monitor coagulation indices (e.g., INR and prothrombin time) frequently to maintain the desired anticoagulant effect.

Diuretics (e.g., potassium-depleting diuretics such as furosemide and thiazide or carbonic anhydrase inhibitors such as acetazolamide): Observe patients closely for the development of hypokalemia.

Mifepristone: The effect of corticosteroids may be reduced for three to four days after taking mifepristone.

Amphotericin-B: Concomitant use of may increase the risk of hypokalemia.

Anticholinergic agents: Acute myopathy has been reported with concomitant use of high doses of corticosteroids and anticholinergics such as neuromuscular blocking agents.

In patients taking corticosteroids, antagonism of the neuromuscular blocking effects of pancuronium and vecuronium may occur. This interaction may be expected with all competitive neuromuscular blockers.

Insulin and Oral Antidiabetic Agents: Corticosteroids such as methylprednisolone may increase blood glucose concentrations and may cause impaired glucose tolerance. Dosage adjustment of antidiabetic agents may be required when these two drugs are used concomitantly.

Digitalis Glycosides: Patients may be at increased risk of arrhythmias due to hypokalemia.

Toxoids and live or inactivated vaccines: Patients on prolonged corticosteroid therapy may exhibit diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS
Pregnancy

Corticosteroids may cause fetal damage (i.e., cleft palate, intrauterine growth retardation and side effects on brain growth and development) and abortion when administered to pregnant animals. Although there is no evidence that the use of corticosteroids result in an increased incidence of congenital abnormalities such as cleft palate in man, corticosteroids may increase the risk of intrauterine growth retardation when administered for long periods or repeatedly during pregnancy.

Women who are pregnant or planning on becoming pregnant while receiving corticosteroids should inform their physician. Methylprednisolone should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Methylprednisolone readily crosses the placenta. Carefully monitor infants born to women who received corticosteroids during pregnancy for symptoms of adrenal insufficiency.

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

Lactation
Corticosteroids are excreted in breast milk. Corticosteroid distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in breastfeeding infants. Methylprednisolone should be administered to a breastfeeding mother only if the potential benefit outweighs the potential risk to the infant.

Children
The efficacy and safety of corticosteroids are considered to be similar in adults and children. Long-term administration of corticosteroids should be avoided in infancy, childhood and adolescence since this may cause growth retardation which may be irreversible.

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

Closely monitor growth and development of infants and children if prolonged therapy is necessary.

There are reports of increased intracranial pressure with papilledema in children (pseudomotor cerebri) usually after treatment withdrawal of methylprednisolone.

UNDESIRABLE EFFECTS
Gastrointestinal Effects: Dyspepsia, diarrhea, esophagitis, peptic ulcer with possible perforation and hemorrhage, abdominal distention, abdominal pain, esophageal ulceration, esophageal candidiasis, pancreatitis, perforation of bowel, gastric hemorrhage, nausea

Musculoskeletal Effects: Arthralgia, muscle atrophy, muscular weakness, myalgia, steroid myopathy, neuropathic arthropathy, avascular osteonecrosis, osteoporosis, pathological fracture, long bone and spinal compression fractures, and tendon rupture (particularly of the Achilles tendon)

Skin and Subcutaneous Tissue Disorders: Impaired wound healing, petechiae, ecchymosis, thin fragile skin, erythema, skin atrophy, striae, hyperhidrosis, hirsutism, telangiectasia, acne, urticaria, rash, and pruritus. Reports of Kaposi's sarcoma occurrence in patients receiving corticosteroid therapy; discontinuation of corticosteroids may result in clinical remission.

Endocrine-Metabolic Effects: Suppression of hypothalamo-pituitary-adrenal (HPA) axis; growth suppression in infants, children and adolescents; development of cushingoid state, increased appetite which may result in weight gain, impaired glucose tolerance, increased requirements for insulin or oral hypoglycemic agents in diabetes, increased appetite, manifestations of latent diabetes mellitus, pituitary unresponsiveness, negative nitrogen and calcium balance

Psychiatric Effects:
Abnormal behavior, affective disorder (including affect lability, depressed mood, euphoric mood, psychological dependence, suicidal ideation), behavioral disturbances (including anxiety, confusional state, insomnia, irritability), mental disorder, mood swings, personality change, psychotic behavior, psychotic disorders (including mania, delusion, hallucination, and aggravation of schizophrenia)

Nervous System Effects: Amnesia, cognitive disorder, convulsions, dizziness, headache, increased intracranial pressure with papilledema (benign intracranial hypertension)

Ophthalmic Effects:
Glaucoma, increased intraocular pressure, posterior subcapsular cataracts, exophthalmos, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal disease

Cardiovascular Effects: Myocardial rupture following recent myocardial infarction,hypertension, hypotension, circulatory collapse

Immune System Effects: Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs, latent infections becoming active, including reactivation of tuberculosis and opportunistic infections, allergic reactions including anaphylactoid reactions, anaphylaxis, and angioedema; may suppress reactions to skin tests

Fluid and Electrolyte Disturbances: Congestive heart failure in susceptible patients, hypokalemic alkalosis, metabolic acidosis, fluid retention, potassium loss, sodium retention, and increased calcium excretion

Investigations:
Elevation of serum liver enzyme levels (alanine transaminase, aspartate transaminase and alkaline phosphatase), hypokalemia, increased calcium excretion/urine calcium increased

Reproductive System and Breast Disorders: Menstrual irregularities and amenorrhea

Ear and labyrinth Disorders: Vertigo, impaired hearing

Others:
Hiccups, leukocytosis, malaise, withdrawal symptoms, and moon face

OVERDOSE AND TREATMENT
As the clinically effective dose of corticosteroids vary according to the indications and requirements of individual patients, it is difficult to define "excessive" dosage of corticosteroids. Reports of acute toxicity and/or death resulting from corticosteroid overdosage are rare. However, continued use of large doses of corticosteroids (which are often necessary to elicit a clinical response) without proper dose reduction, leads to exaggeration of usual corticosteroid-related problems and aggravate pre-existing disease states (i.e., ulceration of the gastrointestinal tract, electrolyte disturbances, infections, diabetes, and edema).

There is no known specific antidote available. Treatment of acute overdose is symptomatic and supportive (including respiratory and cardiovascular function). In case of chronic toxicity, closely monitor fluids and electrolytes levels. Serum levels are not clinically useful.

Methylprednisolone is dialyzable.

STORAGE CONDITIONS
Store at temperatures not exceeding 25°C. Keep the product out of reach and sight of children.

AVAILABILITY
Metcort 4 mg TABLET - box of 100 tablets (in aluminum flex foils)
Metcort 16 mg TABLET - box of 100 tablets (in aluminum flex foils)

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by **ASIAN ANTIBIOTICS, INC.**
No.130 Pioneer Street, Mandaluyong City, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

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