

PHYSICIAN'S PRESCRIBING INFORMATION

METHYLPREDNISOLONE MERCK® 40mg ; 120 mg ; 500 mg ; 1 g

TRADE NAME OF THE MEDICINAL PRODUCT

METHYLPREDNISOLONE MERCK® 40 mg
METHYLPREDNISOLONE MERCK® 500 mg

METHYLPREDNISOLONE MERCK® 120 mg
METHYLPREDNISOLONE MERCK® 1 g

FORM AND PRESENTATION

Vials of freeze-dried powder for solution for injection.

DRUGS-ABOUT.COM

COMPOSITION

- **METHYLPREDNISOLONE MERCK® 40 mg:**
Methylprednisolone hemisuccinate 50.68 mg equivalent to Methylprednisolone 40.00 mg per vial.
Excipients : sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium hydroxide, lactose monohydrate.
- **METHYLPREDNISOLONE MERCK® 120 mg:**
Methylprednisolone hemisuccinate 152.04 mg equivalent to Methylprednisolone 120.00 mg per vial.
Excipients : sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium hydroxide, lactose monohydrate.
- **METHYLPREDNISOLONE MERCK® 500 mg:**
Methylprednisolone hemisuccinate 633.50 mg equivalent to Methylprednisolone 500.00 mg per vial.
Excipients : sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium hydroxide.
- **METHYLPREDNISOLONE MERCK® 1 g:**
Methylprednisolone hemisuccinate 1.267 gram equivalent to Methylprednisolone 1.000 gram per vial.
Excipients : sodium dihydrogen phosphate dihydrate, disodium phosphate dodecahydrate, sodium hydroxide.

ACTIONS

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs 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.

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

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of METHYLPREDNISOLONE MERCK® and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

THERAPEUTIC INDICATIONS

When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the condition.

METHYLPREDNISOLONE MERCK® is indicated for intravenous use in the following conditions:

Endocrine Disorders: Primary or secondary adrenocortical insufficiency (hydrocortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance) ; Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used) ; Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful ; Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected ; Congenital adrenal hyperplasia ; Hypercalcemia associated with cancer ; Nonsuppurative thyroiditis.

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) ; Acute and subacute bursitis ; Epicondylitis ; Acute nonspecific tenosynovitis ; Acute gouty arthritis ; Psoriatic arthritis ; Ankylosing spondylitis.

Collagen Diseases: During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus ; Systemic dermatomyositis (polymyositis) ; Acute rheumatic carditis.

Dermatologic Diseases: Pemphigus ; Severe erythema multiforme (Stevens-Johnson syndrome) ; Exfoliative dermatitis ; Bullous dermatitis herpetiformis ; Severe seborrheic dermatitis ; Severe psoriasis ; Mycosis fungoides.

Allergic States: Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in: Bronchial asthma ; Contact dermatitis ; Atopic dermatitis ; Serum sickness ; Seasonal or perennial allergic rhinitis ; Drug hypersensitivity reactions ; Urticarial transfusion reactions ; Acute noninfectious laryngeal edema (epinephrine is the drug of first choice).

Ophthalmic Diseases: Severe acute and chronic allergic and inflammatory processes involving the eye, such as: Herpes zoster ophthalmicus ; Iritis, iridocyclitis ; Chorioretinitis ; Diffuse posterior uveitis and choroiditis ; Optic neuritis ; Sympathetic ophthalmia ; Anterior segment inflammation ; Allergic conjunctivitis ; Allergic corneal marginal ulcers ; Keratitis.

Gastrointestinal Diseases: To tide the patient over a critical period of the disease in: Ulcerative colitis (systemic therapy) ; Regional enteritis (systemic therapy).

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 pneumonia.

Hematologic Disorders: Acquired (autoimmune) hemolytic anemia ; Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)

Secondary thrombocytopenia in adults ; Erythroblastopenia (RBC anemia) ; Congenital (erythroid) hypoplastic anemia.

Neoplastic Diseases: For palliative management of: Leukemias and lymphomas in adults ; Acute leukemia of childhood.

Edematous States: To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus

Nervous System: Acute exacerbations of multiple sclerosis

Miscellaneous: Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy

Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS

METHYLPREDNISOLONE MERCK® is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and the constituents.

WARNINGS

In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation 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. Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic infections, in any location of 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.

A study has failed to establish the efficacy of METHYLPREDNISOLONE MERCK® in the treatment of sepsis syndrome and septic shock. The study also suggests that treatment of these conditions with METHYLPREDNISOLONE MERCK® may increase the risk of mortality in certain patients (ie, patients with elevated serum creatinine levels or patients who develop secondary infections after METHYLPREDNISOLONE MERCK®).

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, 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, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. 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 cortisone or hydrocortisone 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.

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving nonimmunosuppressive doses of corticosteroids.

The use of METHYLPREDNISOLONE MERCK® 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 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.

Because rare instances of anaphylactic (eg, bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large IV doses of METHYLPREDNISOLONE MERCK® (greater than 0.5 gram administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects 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, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (thread-worm) 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 septicemia.

PRECAUTIONS

General precautions: 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 reinstated. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on 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 manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Steroids should be used with caution in nonspecific 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; and myasthenia gravis.

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

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

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 **POSODOLOGY AND METHOD OF ADMINISTRATION**)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriplegia. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

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.

DRUG INTERACTIONS

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporin and methylprednisolone; therefore, it is possible that adverse events associated with the individual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampin may increase the clearance of methylprednisolone and may require increases in methylprednisolone dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of methylprednisolone and thus decrease its clearance. Therefore, the dose of methylprednisolone should be titrated to avoid steroid toxicity. Methylprednisolone may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when methylprednisolone is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

Information for the Patient

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances ; Sodium retention ; Fluid retention ; Congestive heart failure in susceptible patients ; Potassium loss ; Hypokalemic alkalosis ; Hypertension ; Musculoskeletal ; Muscle weakness ; Steroid myopathy ; Loss of muscle mass ; Severe arthralgia ; Vertebral compression fractures ; Aseptic necrosis of femoral and humeral heads ; Pathologic fracture of long bones ; Osteoporosis ; Tendon rupture, particularly of the Achilles tendon ; Gastrointestinal ; Peptic ulcer with possible perforation and hemorrhage ; Pancreatitis ; Abdominal distention ; Ulcerative esophagitis ; Increases in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase have been observed following corticosteroid treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation. ; Dermatologic ; Impaired wound healing ; Thin fragile skin ; Petechiae and ecchymoses ; Facial erythema ; Increased sweating ; May suppress reactions to skin tests ; Neurological ; Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment ; Convulsions ; Vertigo ; Headache ; Endocrine ; Development of Cushingoid state ; Suppression of growth in children ; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness ; Menstrual irregularities ; Decreased carbohydrate tolerance ; Manifestations of latent diabetes mellitus ; Increased requirements for insulin or oral hypoglycemic agents in diabetics ; Ophthalmic ; Posterior subcapsular cataracts ; Increased intraocular pressure ; Glaucoma ; Exophthalmos ; Metabolic ; Negative nitrogen balance due to protein catabolism.

The following *additional* adverse reactions are related to parenteral corticosteroid therapy: Hyperpigmentation or hypopigmentation ; Subcutaneous and cutaneous atrophy ; Sterile abscess ; Anaphylactic reaction with or without circulatory collapse, cardiac arrest, bronchospasm ; Urticaria ; Nausea and vomiting ; Cardiac arrhythmias; hypotension or hypertension.

POSODOLOGY AND METHOD OF ADMINISTRATION

This proprietary medicinal product is not suitable for inhalation using a nebulizer.

INTRAVENOUS INJECTION

The dosage varies according to the diagnosis, severity of the disease, prognosis, patient response and tolerance of treatment.

The powder is mixed with water for injections and the resulting solution may be administered directly by the slow I.V. route, or by I.V. infusion after dilution in sodium chloride or glucose solution.

When high dose therapy is desired, the recommended dose of METHYLPREDNISOLONE MERCK® is 30 mg/kg administered intravenously over at least 30 minutes. This dose may be repeated every 4 to 6 hours for 48 hours.

In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized; usually not beyond 48 to 72 hours.

Although adverse effects associated with high dose short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.

In other indications initial dosage will vary from 10 to 40 mg of methylprednisolone depending on the clinical problem being treated. The larger doses may be required for short-term management of severe, acute conditions. The initial dose usually should be given intravenously over a period of several minutes. Subsequent doses may be given intravenously at intervals dictated by the patient's response and clinical condition. Corticoid therapy is an adjunct to, and not replacement for conventional therapy.

Dosage may be reduced for infants and children but should be governed more for the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg per kg every 24 hours.

Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

Directions for use, handling instructions

In order to avoid drilling a hole in the closures, it is recommended that a needle with an outside diameter of 0.8 mm or less be used.

Reconstitution of the freeze-dried powder should be done with Sterile Water for Injections

METHYLPREDNISOLONE MERCK® 40 mg: add 2 ml of sterile water for injections.

METHYLPREDNISOLONE MERCK® 120 mg: add 2 ml of sterile water for injections.

METHYLPREDNISOLONE MERCK® 500 mg: add 8 ml of sterile water for injections.

METHYLPREDNISOLONE MERCK® 1 g: add 16 ml of sterile water for injections.

The powder should dissolve within less than 30 seconds. Shake the vial gently if needed.

The reconstituted solutions remain stable for at least 48 hours at temperatures below 25°C. They are not needed to be protected from light.

In view of the risk of bacteriological contamination, however, it is recommended to store this solution at a temperature between +2°C and +8°C.

Israeli Drug License number: METHYLPREDNISOLONE MERCK® 40 mg : 12570.30503 ; METHYLPREDNISOLONE MERCK® 120 mg : 12573.30504 ; METHYLPREDNISOLONE MERCK® 500 mg : 12572.30505 ; METHYLPREDNISOLONE MERCK® 1 g : 12571.30506

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