Solupred

Sterile powder of Methylprednisolone

Composition

Solupred 125 mg Injection: Each vial contains 125 mg of Methylprednisolone as Methylprednisolone Sodium Succinate USP.

Solupred 500 mg Injection: Each vial contains 500 mg of Methylprednisolone as Methylprednisolone Sodium Succinate USP.

Solupred 1 g Injection: Each vial contains 1 g of Methylprednisolone as Methylprednisolone Sodium Succinate USP.

Properties

Methylprednisolone Sodium Succinate, occurs as a white or nearly white, odorless, hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone. Methylprednisolone, is a synthetic glucocorticosteroid and exhibits a strong anti-inflammatory, immunosuppressive and anti-allergic activity.

Pharmacodynamics

Glucocorticoids diffuse across cell membranes, form a complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA (chromatin) and stimulate transcription of mRNA and subsequent protein synthesis of various enzymes thought to be ultimately responsible for the numerous effects of glucocorticoids after systemic use.

Glucocorticoids not only have an important influence on inflammatory and immune processes, but also affect the carbohydrate, protein and fat metabolism. They also act on the cardiovascular system, the skeletal muscles and the central nervous system.

Effect on the inflammatory and immune process:

i. The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are responsible for most of the therapeutic applications. These properties lead to the following results:

- Reduction of immunoactive cells near the inflammation focus
- Reduced vasodilatation
- Stabilization of lysosomal membranes
- Inhibition of phagocytosis
- Reduced production of prostaglandins and related substances.

A dose of 4 mg methylprednisolone has the same glucocorticoid (anti-inflammatory) effect as 20 mg hydrocortisone. Methylprednisolone has only a minimal mineralocorticoid effect (200 mg methylprednisolone is equivalent to 1 mg desoxycorticosterone).

ii. Effect on carbohydrate and protein metabolism:
Glucocorticoids have a protein catabolic action. The liberated amino acids are converted into glucose and glycogen in the liver by means of the gluconeogenesis process. Glucose absorption in peripheral tissues decreases, which can lead to hyperglycemia and glucosuremia, especially in patients who are prone to diabetes.

iii. Effect on fat metabolism:
Glucocorticoids have a lipolytic action. This lipolytic activity mainly affects the limbs. They also have a lipogenetic effect which is most evident on chest, neck and head. All this leads to a redistribution of the fat deposits.

Maximum pharmacologic activity of corticosteroids lays behind peak blood levels, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct actions by the drugs.

Pharmacokinetics

In vivo, cholinesterases rapidly hydrolyze Methylprednisolone Sodium Succinate to free Methylprednisolone.

In man, Methylprednisolone forms a weak dissociate bond with albumin and transcortin. Approximately 40 to 90% of the drug is bound.

Intravenous infusions with 30 mg/kg, administered over 20 minutes or 1 g administered over 30 to 60 minutes lead after approximately 15 minutes to peak Methylprednisolone plasma levels of nearly 20 µg/ml. About 25 minutes after an intravenous bolus injection of 40 mg peak Methylprednisolone plasma values of 42-47 µg/100 ml are measured.

Intramuscular injections of 40 mg give peak Methylprednisolone plasma levels of 34 µg/100 ml after some 120 minutes. Intramuscular injections give lower peak values than intravenous injections. With IM injections plasma values persist for a longer period, with the result that both administration patterns lead to equivalent quantities of Methylprednisolone. The clinical importance of these small differences is probably minimal when we consider the mechanism of action of glucocorticoids. A clinical response is usually observed 4 to 6 hours after administration. The plasma half-life of methylprednisolone sodium succinate is 2.3 to 4 hours and appears to bear no relation to the administration pattern.

Methylprednisolone is a glucocorticoid with a medium-term activity. It has a biological half-life of 12 to 36 hours. The intracellular activity of glucocorticoids results in a clear difference between plasma half-life and pharmacological half-life. Pharmacological activity persists after measurable plasma levels have disappeared. The duration of anti-inflammatory activity of glucocorticoids approximately equals the duration of hypothalamic-pituitary-adrenal (HPA) axis suppression.

Metabolism of Methylprednisolone occurs via hepatic routes qualitatively similar to that of cortisol. The major metabolites are 20 beta-hydroxymethylprednisolone and 20 beta-hydroxy-6alpha-methylprednisolone and are mainly excreted in the urine as glucuronides, sulphates and unconjugated compounds.

Following IV administration of 14 C labeled Methylprednisolone, 75% of the total radioactivity was recovered in the urine in 96 hours, 9% was recovered in human feces after 5 days and 20% in the bile.

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, **Solupred** is indicated for intravenous or intramuscular use in the following conditions:

1. Anti-inflammatory Treatment

a) 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.

b) Collagen Diseases (immune & complex diseases)

During an exacerbation or as maintenance therapy in selected cases of: Systemic lupus erythematosus (and lupus nephritis), acute rheumatic carditis, systemic dermatomyositis (polymyositis).

c) Dermatologic Diseases

Pemphigus, severe erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, bullous dermatitis herpetiformis, severe seborrheic dermatitis, severe psoriasis, mycosis fungoides, urticaria.

d) 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.

e) 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, allergic conjunctivitis, allergic corneal marginal ulcers.

f) Gastrointestinal Diseases

To tide the patient over a critical period of the disease in: Ulcerative colitis (systemic therapy), regional enteritis (systemic therapy).

g) Respiratory Diseases

Pulmonary sarcoidosis, berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, aspiration pneumonitis, exacerbations of chronic obstructive pulmonary disease (COPD), Loeffler's syndrome not manageable by other means, moderate to severe Pneumocystis carinii pneumonia in AIDS patients (as adjunctive therapy when given within the first 72 hours of initial anti-pneumocystis treatment).

h) 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.

2. Immunosuppressive Treatment

a) Organ transplantation

Methylprednisolone in high doses have been used following organ transplantation as part of multifaceted attempts to reduce the rejection phenomenon.

3. Treatment of Hematological & Neoplastic Disorders

a) 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.

b) Neoplastic Diseases

For palliative management of: Leukemias and lymphomas in adults, acute leukemia of childhood, to improve quality of life in patients with terminal cancer.

4. Treatment of Nervous System

a) Cerebral Edema

Administration immediately prior to intracranial surgery and in the immediate postoperative period has reduced the duration of postoperative complications related to cerebral edema.

b) Acute Spinal Cord Injury

The use of methylprednisolone in high dose has resulted in improvement in motor and sensory recovery. Treatment should begin within 8 hours of injury.

c) Acute Exacerbations of Multiple Sclerosis

5, Treatment of Shock States

In severe hemorrhagic, traumatic or surgical shock, adjunctive use of Methylprednisolone IV may aid in achieving hemodynamic restoration.

6, Endocrine Disorders

Primary or secondary adrenocortical insufficiency or acute adrenocortical insufficiency (Hydrocortisone is generally the drug of choice. When mineralocorticoid activity is undesirable, Methylprednisolone may be preferred.) 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, nonsuppurative thyroiditis, hypercalcemia associated with cancer.

7. Miscellaneous

Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy, trichinosis with neurologic or myocardial involvement.

Dosage and administration

Indications	Dosage
Adjunctive therapy in **life-threatening conditions**	**Administer 30 mg/kg IV over a period of at least 30 minutes.** Dose may be repeated every 4 to 6 hours for up to 48 hours.
Acute respiratory distress syndrome (ARDS)	**Initially 2-3 mg/kg/day IV, decreasing after 7 days.**
Rheumatic disorders unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within a week after therapy. **1 g/day for 1 to 4 days, or 1 g/month for 6 months.**
Systemic lupus erythematosus (SLE) unresponsive to standard therapy (or during exacerbation episodes)	**Administer 1 g/day for 3 days as IV pulse dosing over at least 30 minutes.** The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.
Multiple sclerosis unresponsive to standard therapy (or during exacerbation episodes)	**Administer 1 g/day for 3 or 5 days as IV pulse dosing over at least 30 minutes.** The regimen may be repeated if improvement has not occurred within a week after therapy, or as the patient's condition dictates.
Acute spinal cord injury	**Treatment should begin within 8 hours of injury.** • *Within 3 hours of injury:* Bolus 30 mg/kg in 50ml IV fluid over 15 minutes, wait 45 minutes, then continuous infusion of 5.4 mg/kg/hour for 23 hours. • *3-8 hours after injury:* Bolus 30 mg/kg in 50ml IV fluid over 15 minutes, wait 45 minutes, then continuous infusion of 5.4 mg/kg/hour for 47 hours. There should be a separate intravenous site for the infusion pump.
Edematous states, such as **glomerulonephritis** or **lupus nephritis**, unresponsive to standard therapy (or during exacerbation episodes)	Administer either regimen as IV pulse dosing over at least 30 minutes. The regimen may be repeated if improvement has not occurred within 1 week after therapy, or as the patient's condition dictates. **30 mg/kg every other day for 4 days or 1 g/day for 3, 5 or 7 days.**
Terminal cancer (to improve quality of life)	**Administer 125 mg /day IV for up to 8 weeks.**
Chronic obstructive pulmonary disease (COPD)	**125 mg IV every 6 hours for 3 days**, switch to an oral corticosteroid and taper dose. Total treatment period should be at least 2 weeks.
Pemphigus & Bullous Pemphigoid	**20-30 mg/kg IV as pulse therapy depending on patients' conditions.**
In other indications	**Initial dosage will vary from 10 to 500 mg depending on the clinical problem being treated.** The larger dosage may be required for short-term management of severe, acute conditions. The initial dose should be given intravenously over a period of at least 5 minutes (e.g. up to 250 mg) to at least 30 minutes (e.g. doses exceeding 250 mg). Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical conditions.

Dosage may be reduced for infants and children but should be governed more by 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.

Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The "gasping syndrome" has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates.

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. Medical surveillance is also needed in case of interruption of chronic treatment.

Methylprednisolone sodium succinate solution may be administered by intravenous or intramuscular injection or by intravenous infusion. The preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution as directed.

Directions for reconstitution

1. Remove protective plastic flip-off seal.
2. Cleanse stopper with suitable germicide.
3. Aseptically add 2 ml Bacteriostatic Water for Injection for the 125 mg vial or 8 ml Bacteriostatic Water for Injection for the 500 mg vial or 15.6 ml Bacteriostatic Water for Injection for the 1 g vial by means of a syringe into the vial.
4. Shake the vial thoroughly to dissolve the powder content.
5. Withdraw the dose in the usual manner with the help of a syringe; unused portion should be discarded.

Preparation of Solutions for IV Infusion: First prepare the solution for injection as directed. Therapy may be initiated by administering the Methylprednisolone Sodium Succinate solution intravenously over a period of at least 5 minutes (e.g. doses up to and including 250 mg) to at least 30 minutes (e.g. doses exceeding 250 mg). Subsequent doses may be withdrawn and administered similarly.

If desired, the medication may be administered in diluted solutions by admixing the reconstituted product with Dextrose 5% in water, normal saline, dextrose 5% in 0.45% sodium chloride. Dilute concentrations of 0.25 mg/ml or greater dilution are physically and chemically stable for 24 hours. In cases where administration of small volumes of fluids or larger doses of Methylprednisolone Sodium Succinate are desirable, 125 mg to 3000 mg doses in 50 ml solutions of the above diluents are physically and chemically stable for at least 6 hours.

Contraindications

Methylprednisolone Sodium Succinate is contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

Adverse reactions

Systemic adverse reactions may be observed. Although rarely occurring in very short term therapy, they should always be carefully traced. This is part of the follow-up of any corticotherapy and does not specifically pertain to any particular product. These possible adverse reactions of glucocorticoids like Methylprednisolone are:

i) Fluid and Electrolyte Disturbances

Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, hypertension.

ii) 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.

iii) Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage, pancreatitis, abdominal distention and ulcerative esophagitis.

iv) Dermatologic

Impaired wound healing, thin fragile skin, petechiae and ecchymoses, facial erythema, increased sweating, may suppress reactions to skin tests.

v) Neurological

Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, convulsions, euphoria, insomnia, mood swings, vertigo, headache.

vi) 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.

vii) Ophthalmic

Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos.

viii) Metabolic

Negative nitrogen balance due to protein catabolism.

ix) Immune system

Masking infections, may suppress reactions including anaphylaxis.

ix) 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.

Special precautions

> Special risk groups

Patients belonging to the following special risk groups should be under strict medical surveillance and should be treated during an as short as possible period.

- Children: Growth may be suppressed in children receiving long-term, daily-divided doses glucocorticoid therapy. The use of such a regimen should be restricted to those most serious indications.
- Diabetics: Manifestations of latent diabetes mellitus or increased requirements for insulin or oral hypoglycemic agents.
- Hypertensive patients: Aggravation of arterial hypertension.
- Patients with psychiatric antecedents: Existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

>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.

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

>Glucocorticoids 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.

>Data from a clinical study conducted to establish the efficacy of Methylprednisolone Sodium Succinate in septic shock, suggest that a higher mortality occurred in subsets of patients who entered the study with elevated serum creatinine levels or who developed a secondary infection after therapy began.

>The use of Methylprednisolone Sodium Succinate in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the glucocorticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen. If glucocorticoids are indicated in patients with latent tuberculosis or 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 (e.g. bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has history of allergy to any drug.

>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 glucocorticosteroids on patients with hypothyroidism and in those with cirrhosis.

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

>Glucocorticosteroids should be used with caution in nonspecific ulcerative colitis.

>Methylprednisolone sodium succinate should not be used routinely to treat head injury as demonstrated by the results of a multicenter study. The study results revealed an increased mortality in the 2 weeks after injury in patients administered methylprednisolone sodium succinate compared to placebo (1.18 relative risk). A causal association with methylprednisolone sodium succinate treatment has not been established.

>Some of these presentations contain benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "gasping syndrome" (respiratory disorder characterized by a persistent gasping for breath) in premature infants.

>Corticotherapy has to be considered when interpreting a whole series of biological tests and parameters (e.g- skin tests, thyroid hormone levels).

>The duration of the treatment should in general be kept as short as possible. Medical surveillance is recommended during chronic treatment. The discontinuation of a chronic treatment should also occur under medical surveillance (gradual discontinuation, evaluation of the adrenocortical function). The most important symptoms of adrenocortical insufficiency are asthenia, orthostatic hypotension and depression.

>Injection into the deltoid muscle should be avoided because of the high incidence of subcutaneous atrophy.

Incompatibilities

The IV compatibility and stability of methylprednisolone sodium succinate solutions and with other drugs in intravenous admixtures are dependent on admixture PH, concentration, time, temperature and the ability of methylprednisolone to solubilize itself. Thus, to avoid compatibility and stability problems, whenever possible it is recommended that solutions of methylprednisolone sodium succinate be administered separate from other drugs and as either IV push, through and IV medication chamber or as an IV "piggy-back" solution.

Use in pregnancy & lactation

Pregnancy: Methylprednisolone has been shown to be teratogenic in various animal species when given in doses equivalent to the human dose. There are no adequate and well-controlled studies in pregnant women. Methylprednisolone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which methylprednisolone has been given to pregnant rodents and rabbits have yielded an increased incidence of cleft palate in the offspring. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Lactation: Methylprednisolone is excreted in breast milk. Caution should be exercised when methylprednisolone is administered to a nursing woman.

Drug interactions

Desired interactions

- Prevention of nausea and vomiting associated with cancer chemotherapy.
- Mild to moderately emetogenic chemotherapy: For an increased effect, a chlorinated phenothiazine may be used with the first dose methylprednisolone (one hour before chemotherapy).
- Severely emetogenic chemotherapy: For an increased effect, metoclopramide or a butyrophenon may be used with the first dose methylprednisolone (one hour before chemotherapy).
- By the treatment of fulminating or disseminated pulmonary tuberculosis and tuberculous meningitis with subarachnoid block or impending block, methylprednisolone is used concurrently with appropriate antituberculous chemotherapy.
- By the treatment of neoplastic diseases like leukemia and lymphoma, methylprednisolone is usually used in conjunction with an alkylating agent, an antimetabolite and a vinca-alkaloid.

Undesired interactions

- Combination of glucocorticosteroids with ulcerogenic drugs (e.g. salicylates and NSAID) increases the risk of gastrointestinal complications.
- Combination of glucocorticosteroids with thiazid-diuretics increases the risk of glucose intolerance. Glucocorticosteroids can increase the requirements for insulin or oral hypoglycemic agents in diabetics.
- 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 possible hazards of neurological complications and/or lack of antibody response.
- Acetylsalicylic acid should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.
- Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Concurrent administration of these agents results in a mutual inhibition of metabolism. Therefore it is possible that convulsions and other adverse events associated with the individual use of either drug may be more appropriate to occur.

Overdose

There is no clinical syndrome of acute overdosage with methylprednisolone sodium succinate. Chronic overdosage induces typical Cushing symptoms. Methylprednisolone is dialysable.

Storage

Protect from light. Store unreconstituted product at controlled room temperature 20° to 25°C. Store reconstituted solution with Bacteriostatic WFI at 20° to 25°C. Use solution within 48 hours after mixing.

Packaging

Solupred 125 mg Injection: Each box contains 1 vial Methylprednisolone Sodium Succinate with 1 vial of 2 ml Bacteriostatic Water for Injection in blister pack & a 3 ml sterile disposible syringe.

Solupred 500 mg Injection: Each box contains 1 vial Methylprednisolone Sodium Succinate with 1 vial of 8 ml Bacteriostatic Water for Injection in blister pack & a 10 ml sterile disposible syringe.

Solupred 1 g Injection: Each box contains 1 vial Methylprednisolone Sodium Succinate with 1 vial of 15.6 ml Bacteriostatic Water for Injection each in blister pack & a 20 ml sterile disposible syringe.

Manufactured by

ZISKA PHARMA

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