℞ *For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.*

Methylprednisolone Sodium Succinate for Injection USP

VARPRED®-S 500 mg

Each vial contains:
Methylprednisolone Sodium Succinate USP
eq. to Methylprednisolone 500 mg

VARPRED®-S 1 g

Each vial contains:
Methylprednisolone Sodium Succinate USP
eq. to Methylprednisolone 1 gm

DESCRIPTION:
Methylprednisolone sodium succinate is a white or nearly white odourless, hygroscopic amorphous solid, MP (228° to 237°C), pKa of 4.6, partition coefficient (butyronitrile-water) of 0.03 at pH 8.5, very soluble in water and in alcohol, slightly soluble in acetone and practically insoluble in chloroform and ether. The chemical name is Pregna-1,4-diene-3,20-dione, 21-(3-carboxy-1-oxopropoxy)11,17-dihydroxy-6-methyl-, monosodium salt, (6α,11β)-;11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20dione 21- (sodium succinate). The chemical formula is C26H33NaO8 and its molecular weight is 496.53 g/mol.

THERAPEUTIC INDICATIONS:
Intravenous administration of Methylprednisolone Sodium Succinate for Injection is indicated in situations, in which a rapid and intense hormonal effect is required.
Methylprednisolone Sodium Succinate for Injection is indicated for:

- Hypersensitivity and dermatologic conditions
  - Status asthmaticus
  - Anaphylactic reactions
  - Drug reactions
  - Contact dermatitis
  - Urticaria
  - Generalized neurodermatitis
  - Reactions to insect bites
  - Pemphigus foliaceous and vulgaris
  - Exfoliative dermatitis
  - Erythema multiforme
- In anaphylactic reactions epinephrine or norepinephrine should be administered first for an immediate hemodynamic effect followed by intravenous injection of Methylprednisolone Sodium Succinate for Injection and other accepted procedures. There is evidence that the corticoids through their prolonged hemodynamic effect are of value in preventing recurrent attacks of acute anaphylactic reactions.
- In sensitivity reactions such as in serum sickness, allergic dermatosis (urticaria) and reactions to insect bites, Methylprednisolone Sodium Succinate for Injection is capable of providing relief within 1/2 to 2 hours. In some asthmatic patients it may be advantageous to administer Methylprednisolone Sodium Succinate for Injection by slow intravenous drip over a period of hours.
  - As adjunctive therapy in
  - Acute systemic lupus erythematosus
  - Acute rheumatic fever
  - Acute gout

In these conditions Methylprednisolone Sodium Succinate for Injection may be given by slow intravenous administration over a period of several minutes. Thereafter, the patient should be placed on intramuscular or oral therapy as required for continued relief of symptoms. In these conditions, other accepted measures of therapy should also be instituted.

- **Ulcerative colitis:** Colonic instillation of methylprednisolone sodium succinate in retention enemas or by continuous drip, have been shown to be a useful adjunct in the treatment of patients with ulcerative colitis.
- **Shock:** In severe haemorrhagic or traumatic shock, adjunctive use of intravenous Methylprednisolone Sodium Succinate for Injection may aid in achieving hemodynamic restoration. Corticoid therapy should not replace standard methods of combating shock, but present evidence indicates that concurrent use of large doses of corticoids with other measures may improve survival rates.
- **Organ transplants:** Corticosteroids, both parenterally and orally, in high doses have been used following organ transplantation as part of multi-faceted attempts to reduce the rejection phenomenon.
- Methylprednisolone Sodium Succinate for Injection is suitable for such indications.

Cerebral oedema of non-traumatic origin Administration of methylprednisolone sodium succinate immediately prior to intracranial surgery and in the immediate post-operative period has reduced the duration of postoperative complications related to cerebral oedema.
Paediatrics: Methylprednisolone Sodium Succinate for Injection is contraindicated for use in premature infants (see Contraindications) and should be used with caution in the paediatric population (see Special Warnings and Precautions & Special Population).
Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology
Dosing Considerations:

- Because complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.
- The lowest possible dose of corticosteroid should be used to control the condition under treatment.
- Patients should be advised to inform subsequent health professionals of the prior use of methylprednisolone sodium succinate.
- The existence of diabetes, osteoporosis, renal insufficiency, chronic psychosis, cardiovascular disease, myasthenia gravis or predisposition to thrombophlebitis requires that Methylprednisolone Sodium Succinate for Injection be administered with extreme caution.
- Dosage adjustments may be required based on the following:
  - during remission
  - exacerbation of the disease process
  - the patient's individual response to therapy
  - upon exposure of the patient to emotional or physical stress such as serious infection, surgery or injury. Methylprednisolone Sodium Succinate for Injection dosage may need to be increased during and after the stressful situation.
- **Geriatrics:** In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
- Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increased risk for osteoporosis, as well as increased risk for fluid retention with possible resultant hypertension.
- **Paediatrics:** Methylprednisolone Sodium Succinate for Injection is contraindicated for use in premature infants (see Contraindications) and should be used with caution in the paediatric population (see Special Warnings and Precautions & Special population).

Recommended Dose and Dosage Adjustment

- Corticosteroid therapy is an adjunct to, and not replacement for, conventional therapy.
- As adjunctive therapy in life threatening conditions (e.g., shock states), the recommended dose of Methylprednisolone Sodium Succinate for Injection is 30 mg per kg, given intravenously over a period of at least 30 minutes. This large dose may be repeated every 4 -6 hours for up to 48 hours.
- In other indications, initial dosage will vary from 10 to 500 mg depending on the clinical problem being treated. Larger doses may be required for short-term management of severe, acute conditions. Therapy may be initiated by administering Methylprednisolone Sodium Succinate for Injection intravenously over a period of at least 5 minutes (e.g., doses up to 250 mg) to at least 30 minutes (e.g., doses greater than 250 mg). Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition.
- Methylprednisolone Sodium Succinate for Injection in doses of 40 to 120 mg administered as retention enemas or by continuous drip three to seven times weekly for periods of two or more weeks have been shown to be a useful adjunct in the treatment of some patients with ulcerative colitis. Many patients can be controlled with 40 mg of methylprednisolone sodium succinate administered in from 1 to 10 fluid ounces of water depending on the degree of involvement of the inflamed colonic mucosa. Other accepted therapeutic measures should, of course, be instituted.

Method of administration
Methylprednisolone Sodium Succinate for Injection may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection.
To administer Methylprednisolone Sodium Succinate for Injection, reconstitute the vial as per instructions.
Don't use if any Particle, leakage or breakage found.
Directions for reconstitution:

- Remove the protective plastic flip-top seal.
- Swab the rubber stopper with an antiseptic solution and introduce the required quantity of the diluent by means of a syringe into the vial.
- Shake the vial thoroughly to dissolve the powder content.
- Withdraw the dose in the usual manner with the help of a syringe.

Reconstitute with Sterile Water for Injection, or, if required, Bacteriostatic Water for Injection as follows:
Reconstitution Table

Size	Quantity of Diluent (mL)	Approx. Withdrawable Volume (mL)	Nominal Concentration (mg/mL)
500 mg/vial	7.8	8	62.5
1000 mg/vial	15.6	16	62.5

The reconstituted and diluted solution should be inspected visually for discolouration, haziness, particulate matter and leakage prior to administration. Discard unused portion.
Preparation of solution for IM or IV injection: Loosen powder. Hold vial horizontally and rotate while directing the stream of diluent against the wall of the vial. Shake vial gently after all the diluent is added. Use solution only if it is clear.
Preparation of solutions for IV infusion: First prepare the solution for injection as directed. If desired, the medication may be administered in dilute solutions by admixing the reconstituted product with Dextrose 5% in Water, 0.9% Sodium Chloride, Dextrose 5% in 0.45% Sodium Chloride. Concentrations of 0.25 mg/mL or less are physically and chemically stable for 48 hours at 15°C to 25°C. Parenteral drug products should be inspected visually for particulate matter and discolouration, prior to administration, whenever solution and container permit.
Compatibility: The compatibility and stability of Methylprednisolone Sodium Succinate for Injection in solutions and with other drugs in intravenous admixtures is dependent on admixture pH, concentration, time, temperature, and ability of methylprednisolone to solubilize itself. Thus, to avoid compatibility and stability problems, whenever possible it is recommended that Methylprednisolone Sodium Succinate for Injection be administered separate from other drugs and as either IV push, through an IV medication chamber, or as an IV “piggy-back” solution.

CONTRAINDICATIONS:
Methylprednisolone Sodium Succinate for Injection is contraindicated:
- in patients with known hypersensitivity to the ingredients. Methylprednisolone Sodium Succinate for Injection, 40 mg, include lactose produced from cow's milk. This dosage form is therefore contraindicated in patients with a known or suspected hypersensitivity to cow's milk or its components or other dairy products because it may contain trace amounts of milk ingredients.
- for systemic fungal infections
- in patients administered with live or live, attenuated vaccines while receiving immunosuppressive doses of corticosteroids.
- for intrathecal or epidural administration. Reports of serious medical events have been associated with these routes of administration.
- for use in premature infants, as the Bacteriostatic Water for Injection that is indicated for reconstituting Methylprednisolone Sodium Succinate for Injection Plain Vials products contains benzyl alcohol. (see Special Warnings and Precautions & Special Population)
- for intramuscular administration in idiopathic thrombocytopenic purpura.

Except for short-term emergency therapy, Methylprednisolone Sodium Succinate for Injection is contraindicated in patients with:
- arrested tuberculosis
- herpes simplex keratitis
- acute psychoses
- Cushing's syndrome
- peptic ulcer
- markedly elevated serum creatinine
- vaccinia and varicella

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
General: Methylprednisolone Sodium Succinate for Injection should not be administered by any route other than intramuscular injection, intravenous injection or by intravenous infusion.
It is critical that, during administration of Methylprednisolone Sodium Succinate for Injection, appropriate technique be used and care taken to assure proper route of administration.
Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days.
Patients should be advised to inform subsequent health professionals of the prior use of methylprednisolone sodium succinate.
The slower rate of absorption by intramuscular administration should be recognized.
Carcinogenesis and Mutagenesis: Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy.
Discontinuation of corticosteroids may result in clinical remission.
Animal studies found corticosteroids to have possible tumorigenic and mutagenic potential.
Cardiovascular: There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large intravenous doses of methylprednisolone sodium succinate (greater than 0.5 g 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.
Literature reports suggest an apparent association between the use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.
Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result, corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.
As sodium retention with resultant oedema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution, and only if strictly necessary, in patients with congestive heart failure. Corticosteroids should be used with caution in hypertension, or renal insufficiency.
Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed.
Endocrine and Metabolism: Corticosteroid administration may result in hypothalamic-pituitary-adrenal (HPA) axis suppression (secondary adrenocortical insufficiency). 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 may need to be reinstituted. Acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly. Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease. Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus. There is an enhanced effect of corticosteroids in patients with hypothyroidism. Pheochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids, including methylprednisolone. Corticosteroids should only be administered to patients with suspected or identified Pheochromocytoma after an appropriate risk/benefit evaluation.
Gastrointestinal: Glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. In combination with NSAIDs, such as Aspirin (acetylsalicylic acid), the risk of developing gastrointestinal ulcers is increased.
Hematologic: Aspirin (acetylsalicylic acid) should be used cautiously in conjunction with corticosteroids in hypoprothrombinaemia.
Hepatic/Biliary/Pancreatic: Drug-induced liver injury such as acute hepatitis can result from cyclical pulsed intravenous methylprednisolone (usually at initial dose ≥ 1gm/day). The time to onset of acute hepatitis can be several weeks or longer. Resolution of the adverse event has been observed after treatment was discontinued. There is an enhanced effect of corticosteroids in patients with cirrhosis. High doses of corticosteroids may produce acute pancreatitis.
Immune: Corticosteroids may suppress the immune system and may mask some signs of infection, and new infections may appear during their use. Recent studies suggest that corticosteroids should not be used in septic shock (an unapproved indication), and suggest that increased mortality may occur in some subgroups at higher risk (e.g., elevated serum creatinine greater than 2.0 mg/dl or secondary infections). Do not use intra-articularly, intrabursally or for intratendinous administration for local effect in the presence of acute local infection.
Fungal infections: Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.
Special Pathogens: Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Toxoplasma. It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhoea. Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyper infection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia. Corticosteroids should not be used in cerebral malaria. There is currently no evidence of benefit from steroids in this condition. 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.
Vaccination: Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids (Contraindications). Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non immunosuppressive doses of corticosteroids. 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 in high doses, because of possible hazards of neurological complications and lack of antibody response.
Viral infections: Chicken pox and measles can have a more serious or even fatal course in paediatric and adult patients on corticosteroids. In paediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. 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 immune globulin (IG) may be indicated. If chicken pox develops, treatment with antiviral agents should be considered. Recent studies do not support Methylprednisolone Sodium Succinate for Injection use during septic shock, and suggest that increased mortality may occur in some subgroups at higher risk (e.g., elevated serum creatinine greater than 2.0 mg/dl or secondary infections).
Monitoring and Laboratory Tests: Corticosteroids may suppress reactions to skin tests. Since methylprednisolone suppresses endogenous adrenocortical activity, it is highly important that the patient receiving Methylprednisolone Sodium Succinate for Injection be under careful observation, not only during the course of treatment but for some time after treatment is terminated. Monitoring for signs and symptoms of drug-induced secondary adrenocortical insufficiency may be necessary for up to one year following cessation of long-term or high-dose corticosteroid therapy.
Musculoskeletal: Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (e.g., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in paediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy. Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.
Neurologic: Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse events associated with the individual use of either drug may be more apt to occur. Systemic corticosteroids are not indicated for, and therefore should not be used to treat traumatic brain injury. A multicentre study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone sodium succinate compared to placebo. Corticosteroids should be used with caution in patients with seizure disorders. Corticosteroids should be used with caution in patients with myasthenia gravis. There have been reports of epidural lipomatosis in patients taking corticosteroids (including reports in children).
Ophthalmologic: The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.
Psychiatric: Psychological effects have been reported upon withdrawal of corticosteroids; the frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms develop in the patient, especially if depressed mood or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids.
Renal: Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone. Corticosteroids should be used with caution in patients with renal insufficiency.

DRUG INTERACTION WITH OTHER MEDICINAL PRODUCTS:
Methylprednisolone has a wide spectrum of clinical use and is therefore used with numerous concurrent drugs. The interactions summarised below are of known or likely clinical significance. The need for dosage adjustment of either medication will depend on the clinical situation, the dose regimen prescribed and the observed clinical response. The interactions listed have either pharmacokinetic or Pharmacodynamic basis.

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is metabolised mainly by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyses 6ß-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of which (as well as other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 Inhibitors: Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance, resulting in increased plasma concentration of methylprednisolone. Coadministration of CYP3A4 inhibitors may require titration of methylprednisolone dosage to reduce the risk of adverse effects and avoid steroid toxicity.

CYP3A4 inhibitors include:

- Antifungals such as ketoconazole and Itraconazole.
- Antiemetic's such as aprepitant and fosaprepitant.
- Immunosuppressant such as ciclosporin. Mutual inhibition of metabolism occurs with concurrent use of ciclosporin and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon coadministration. Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.
- Macrolide antibacterial such as clarithromycin and erythromycin.
- HIV-protease inhibitors such as ritonavir, may increase plasma concentrations of corticosteroids. Corticosteroids may induce the metabolism of HIV-protease inhibitors, resulting in reduced plasma concentrations.
- Calcium channel blockers such as diltiazem.
- Isoniazid. In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid.
- Oral contraceptives such as ethinylestradiol and norethisterone, retard the metabolism of corticosteroids due to increased binding to globulin, resulting in increased plasma levels of corticosteroids and potentiating their biological effect. The dose of corticosteroids may need to be adjusted when commencing or stopping oral contraceptive therapy.
- Grapefruit juice.

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

CYP3A4 inducers include:

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

CYP3A4 Substrates: In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration. Most CYP3A4 inhibitors are also CYP3A4 substrates.

- Immunosuppressant such as cyclophosphamide and tacrolimus.

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

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

Anticholinergics: Corticosteroids may influence the effect of anticholinergics. Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.

Anticholinesterases: Steroids may reduce the effects of anticholinesterases in myasthenia gravis.

Anticoagulants (Oral) - Vitamin K Antagonists: The effect of methylprednisolone on vitamin K antagonists (e.g., warfarin) is variable. There are reports of enhanced as well as diminished effects of these anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices (such as INR or prothrombin time) should be monitored to maintain the desired anticoagulant effects.

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

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

Diuretics and Other Potassium Depleting Agents: Excessive potassium loss may be experienced with concurrent use of corticosteroids and potassium depleting diuretics (such as furosemide and thiazides) or carbonic anhydrase inhibitors (such as acetazolamide). Patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthine's or beta2 agonists.

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

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

Methylprednisolone may increase the renal clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity.

Somatropin: Concomitant administration may inhibit the growth promoting effect of somatropin.

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

Vaccines: Live vaccines should not be given to individuals with impaired immune responsiveness.

The antibody response to other vaccines may be diminished.

PREGNANCY, LACTATION AND FERTILITY:

Pregnancy: Corticosteroids readily cross the placenta. Corticosteroids have been shown to be teratogenic. Corticosteroids readily cross the placenta. An increased incidence of low birth weights in infants born of mothers receiving corticosteroids has been reported. In humans, the risk of low birth weight appears to be dose related and may be minimised by administering lower corticosteroid doses. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency, although neonatal adrenal insufficiency is rarely reported in infants exposed in utero to corticosteroids. There are no known effects of corticosteroids on labour and delivery. Cataracts have been observed in infants born to mothers treated with long-term corticosteroids during pregnancy.

Lactation: Corticosteroids are excreted in breast milk. Corticosteroids in breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. This medicinal product should only be used while breastfeeding following careful evaluation of the ratio of benefits to risks for the mother and the infant.

Fertility: Steroids may increase or decrease motility and number of spermatozoa in some patients.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

The effect of corticosteroids on the ability to drive or use machinery has not been systematically evaluated. Undesirable effects, such as dizziness, vertigo, visual disturbances, and fatigue are possible after treatment with corticosteroids. If affected, patients should not drive or operate machinery.

UNDESIRABLE EFFECTS

The following Adverse Reactions have been reported with the systemic use of methylprednisolone sodium succinate and other corticosteroid preparations.

System Organ Class	Undesirable Effect
Blood and lymphatic system disorders	Leukocytosis
Infections and infestations	Infection; opportunistic infection; injection site infections following non-sterile administration; decreased resistance to infection
Immune system disorders	Drug hypersensitivity; (anaphylactoid reaction; anaphylactic reaction (with or without circulatory collapse))
Endocrine disorders	Cushingoid; hypopituitarism; hypothalamic pituitary adrenal axis suppression; steroid withdrawal syndrome; moon face; abnormal fat deposits; glycosuria; hypertrichosis; secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness). A steroid “withdrawal syndrome,” seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.
Metabolism and nutrition disorders	Lipomatosis; sodium retention; sodium excretion; fluid retention; alkalosis hypokalemic; dyslipidemia; metabolic acidosis; glucose tolerance impaired; increased requirement for insulin (or oral hypoglycemic agents in diabetics); nitrogen balance negative (due to protein catabolism); blood urea increased; increased appetite (which may result in weight increased); diuresis
Psychiatric disorders	Affective disorder (including affect lability, depressed mood, euphoric mood, drug dependence, suicidal ideation); psychotic disorder (including mania, delusion, hallucination, schizophrenia [aggravation of]); mental disorder; insomnia; mood swings; personality change; confusional state; abnormal behavior; anxiety; irritability; emotional instability
Nervous system disorders	Epidural lipomatosis; intracranial pressure increased (with papilloedema [idiopathic intracranial hypertension] usually following discontinuation of treatment); convulsion; amnesia; cognitive disorder; dizziness; headache; seizures; neuritis; neuropathy; paresthesia
Eye disorders	Central serous chorioretinopathy; cataract; glaucoma; exophthalmos; rare instances of blindness associated with periocular injections.
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Cardiac failure congestive (in susceptible patients); arrhythmia; cardiac arrest; bradycardia; tachycardia; cardiac enlargement; circulatory collapse; hypertrophic cardiomyopathy in premature infants; myocardial rupture following recent myocardial infarction; pulmonary oedema; syncope

Vascular disorders	Hypertension; hypotension; thromboembolism; thrombophlebitis, thrombosis, vasculitis
Respiratory disorders	Hiccups; bronchospasm, pulmonary embolism
Gastrointestinal disorders	Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer hemorrhage); intestinal perforation; gastric hemorrhage; pancreatitis; esophagitis ulcerative; oesophagitis; abdominal distension; abdominal pain; diarrhoea; dyspepsia; nausea; vomiting; dysgeusia; peritonitis (peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis)
Hepatic disorders	Hepatomegaly, hepatitis, drug-induced liver injury, liver failure
Skin and subcutaneous disorders	Angioedema; hirsutism; petechiae; ecchymoses; skin atrophy; erythema; hyperhidrosis; skin striae; rash; pruritus; urticaria; acne; skin hypopigmentation; skin hyperpigmentation; allergic dermatitis; burning or tingling (especially in the perineal area after intravenous injection); cutaneous and subcutaneous atrophy; dry scaly skin; sterile abscess; thinning scalp hair; Kaposi's sarcoma
Musculoskeletal and connective tissue disorders	Muscular weakness; myalgia; myopathy; muscle atrophy; osteoporosis; osteonecrosis; pathological; fracture; neuropathic arthropathy; arthralgia; growth retardation
Reproductive system and breast disorders	Menstruation irregular; increased or decreased motility and number of spermatozoa.
General disorders and administration site conditions	Impaired healing; fatigue; malaise; injection site reaction; oedema peripheral
Investigations	Urine calcium increased; blood potassium decreased; Carbohydrate tolerance decreased; intraocular pressure increased; aminotransferase increased; aspartate aminotransferase increased; blood alkaline phosphatase increased; suppression of reactions to skin tests; post injection flare (following intra-articular use); blood urea increased
Injury, poisoning and procedural complications	Spinal compression fracture; tendon rupture (particularly of the Achilles tendon)

OVERDOSE:
Treatment of acute overdosage is by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of the corticosteroid may be reduced only temporarily, or alternate day treatment may be introduced. Continuous overdosage would require careful gradual reduction of dosage in order to prevent the occurrence of acute adrenal insufficiency. Methylprednisolone is dialyzable.
For management of a suspected drug overdose, contact your regional poison control centre.

PHARMACOLOGICAL PROPERTIES:
Pharmacotherapeutic group:
ATC code: B01AB01
Pharmacodynamic properties:
Methylprednisolone is a potent anti-inflammatory steroid. It has a 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 Sodium Succinate 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.
Methylprednisolone sodium succinate has been investigated for acute spinal cord injury in two randomised, double-blind, comparative National Acute Spinal Cord Injury Studies (NASCIS 2 and 3). The effect of high dose methylprednisolone sodium succinate given as initial bolus of 30 mg/kg by IV for 15 minutes followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 24 hours was significant on neurologic recovery when given to patients within 8 hours from injury (NASCIS 2) and motor recovery was higher for those patients initiated within 3 to 8 hours from injury and treated with the same regimen for 48 hours (NASCIS 3).
Pharmacokinetic Properties:
Methylprednisolone pharmacokinetics is linear, independent of route of administration.
Absorption: After an intravenous infusion of Methylprednisolone Sodium Succinate for Injection, 30 mg/kg over a 20-minute period or 1 g over 30 to 60 minutes, peak methylprednisolone plasma concentrations of approximately 20 mcg/mL were achieved. Peak methylprednisolone levels of 42-47 mcg/100mL were reported following a single 40 mg IV bolus injection to six adult male volunteers. Peak methylprednisolone plasma levels of 33.67 mcg/100 mL were achieved in two hours after a single 40 mg IM injection to 22 adult male volunteers. Although with intramuscular (IM) injection lower peak levels are obtained than with intravenous (IV) injection, the plasma levels persist longer such that the extent of methylprednisolone absorption is equivalent with either route of administration.
Distribution: Methylprednisolone is widely distributed throughout the body and is described by a two-compartment model. Its apparent volume of distribution is approximately 1.4 L/kg and its total clearance is approximately 5 to 6 mL/min/kg.
Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.
Methylprednisolone Sodium Succinate for Injection readily crosses the blood-brain barrier into the central nervous system with peak CSF levels being 5-6% of the corresponding plasma levels. Methylprednisolone peak CSF levels occurred within five minutes to one hour after IV administration of a 500 mg dose to patients with lupus cerebritis.
Methylprednisolone and the sodium succinate salt crosses the placental barrier. Although there is no data regarding methylprednisolone passage into breast milk of humans, it is present in breast milk of animals.
Biotransformation: The sodium succinate ester of methylprednisolone, is rapidly and extensively hydrolysed in vivo by cholinesterase to free methylprednisolone.
In humans, methylprednisolone is metabolised in the liver to inactive metabolites, the major ones being 20a-hydroxymethylprednisolone and 20ß-hydroxymethylprednisolone.
Metabolism in the liver occurs primarily via the CYP3A4. For a list of drug interactions based on CYP3A4-mediated metabolism (see Drug Interaction with Other Medicinal Products).
Elimination: The mean elimination half-life ranges for total methylprednisolone is in the range of 1.8 to 5.2 hours.
The plasma protein binding of methylprednisolone in humans is approximately 77%.
Total body clearance following intravenous or intramuscular injection of methylprednisolone to healthy adult volunteers is approximately 15-16 L/hr. In adult volunteers receiving 40 mg Methylprednisolone Sodium Succinate for Injection, either IM or IV, renal clearance is 0.61-0.83 L/hr. Methylprednisolone clearance is altered by concurrent administration of erythromycin, rifampicin, anticonvulsants, and theophylline.
Following IV administration of radiolabelled 6α-methylprednisolone to six cancer patients, 75% of total reactivity was recovered in the urine after 96 hours and 9% in the faeces after five days. Twenty percent of the total dose was excreted in the bile, but the time course was not cited.

STORAGE:
Store at temperature not exceeding 25ºC in a cool dry place. Protect from light.
Don't use Methylprednisolone Sodium Succinate after the expiry date printed on label and carton.
Keep out of reach of children.

PRESENTATION:
VARPRED-S 500
Primary Packing: 10 ml glass vial USP Type-I.
Secondary Packing: Each vial and 10 ml WFI are placed in the printed mono carton along with package insert.

VARPRED-S 1000
Primary Packing: 20 ml glass vial USP Type-I.
Secondary Packing: Each vial and 20 ml WFI are placed in the printed mono carton along with package insert.

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