SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE PRODUCT

PREDNOL-L® 40 mg lyophilized powder for injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lyophilized injection ampoule;

Active Ingredient:

Contains 53 mg methylprednisolone sodium succinate, equivalent to 40 mg methylprednisolone. The solvent ampoule contains 2 ml of water for injection.

Excipient(s):

Sodium phosphate dibasic (anhydrous) …… 1.5 mg
Lactose Monohydrate (obtained from cow's milk) ……10 mg
Sodium Chloride ……..... 1 mg
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Lyophilized ampoule for injection.

White lyophilized mass in colorless ampoule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PREDNOL-L is indicated to treat any condition in which rapid and intense corticosteroid effect is required such as:

Endocrine diseases: Primary and secondary adrenal insufficiency (hydro-cortisone or cortisone is the first option; synthetic analogues can be used together with mineralocorticoids in necessary cases; mineralocorticoid supplement is of special importance in infants), acute adrenocortical insufficiency, congenital adrenal hyperplasia, cancer-related hypercalcemia, nonsuppurative thyroiditis.

Rheumatic diseases: To be given as an adjunct therapy for a short time (so that the patient can survive an acute event or exacerbation): Rheumatoid arthritis (including low-dose applications and juvenile rheumatoid arthritis), psoriatic arthritis, ankylosing spondylitis, acute gouty arthritis, posttraumatic osteoarthritis, acute nonspecific tenosynovitis, acute and subacute bursitis and epicondylitis, osteoarthritis synovitis.

Collagen tissue diseases: During an exacerbation or in selected cases as a maintenance treatment: Systemic lupus erythematosus, systemic dermatomyositis (polymyositis), acute rheumatic carditis.

Skin diseases: Pemphigus, severe erythema multiforme (Stevens-Johnsons syndrome), exfoliative dermatitis, bullous dermatitis herpetiformis, severe psoriasis, severe seborrheic dermatitis and mycosis fungoides.

Allergic reactions: To control severe or obstructive allergic conditions that do not heal despite sufficient traditional treatment: Bronchial asthma, contact dermatitis, atopic dermatitis, serum sickness, seasonal or perennial allergic rhinitis, drug hypersensitivity reactions, urticarial transfusion reactions, and acute non-infectious laryngeal edema.

Eye diseases: Severe, acute or chronic, allergic or inflammatory disorders of the eye and surrounding tissues: Herpes zoster ophthalmicus, iritis, iridocyclitis, chorioretinitis, common posterior uveitis and choroiditis, optic neuritis, sympathetic ophthalmia, anterior segment inflammation, allergic conjunctivitis, allergic corneal marginal ulcer and keratitis.

Gastrointestinal diseases: In order to survive a critical period of the disease: Ulcerative colitis (systemic therapy) and regional enteritis (systemic therapy).

Respiratory system diseases: Symptomatic sarcoidosis, berilliosis, Löffler syndrome which cannot be treated by other methods, fulminant or disseminated pulmonary tuberculosis together with aspiration pneumonia and necessary antituberculosis treatment.

Hematological diseases: Acquired (autoimmune) hemolytic anemia, secondary thrombocytopenia in adults, erythroblastopenia (red blood cell anemia), congenital (erythroid) hypoplastic anemia, idiopathic thrombocytopenic purpura in adults (IV administration only, IM application is contraindicated).

Neoplastic diseases: for palliative treatments of leukemia and lymphoma in adults, acute leukemia in childhood.

Edema states: Reducing proteinuria or increasing diuresis in nephrotic syndrome caused by non-uremic idiopathic type or lupus erythematosus.

Nervous system disorders: Acute exacerbation of multiple sclerosis.

Shocks that do not respond to standard acute shock therapy: Cardiogenic shock, septic shock, anaphylactic shock, hypovolemic shock, mixed shock situations, trauma, burns, late shocks with various etiological causes and acute spinal cord traumas.

Other: When used in conjunction with appropriate antituberculosis chemotherapy, tuberculosis meningitis with subarachnoid block or block that may develop and, trichinosis containing neurological or myocardial symptoms.

4.2. Posology and route of administration

Posology/Administration frequency and duration:

The recommended dose as an adjunct therapy in life-threatening situations is 30 mg/kg methylprednisolone sodium succinate given intravenously for at least 30 minutes. This dose can be repeated every 4-6 hours up to 48 hours.

If the diseases responding to corticosteroid worsen and/or do not respond to standard therapy, the recommended dosage schedule for high dosing is as follows:

- Rheumatic diseases: 1, 2, 3 or 4 days IV 1 g/day or 6 months IV 1 g/month.
- Systemic lupus erythematosus: 3 days IV 1 g/day.
- Multiple sclerosis: 3 days IV 1 g/day or 5 days IV 1 g/day.
- Edematous conditions such as glomerulonephritis, lupus nephritis: IV 30 mg/kg every day for 4 days, or IV 1 g/day for 3, 5 or 7 days.

Dosing should be done for at least 30 minutes and can be repeated if improvement is not observed within one week after treatment or if deemed necessary according to the patient's condition.

Cancer in terminal period - Quality of life.

Prospective controlled studies have shown that the quality of life of cancer patients in the terminal period is significantly increased by administering 125 mg of methylprednisolone sodium succinate intravenously for up to eight weeks.

Prevention of nausea and vomiting has been associated with cancer chemotherapy. Recommended dosing: light to moderate emetogenic chemotherapy: 250 mg methylprednisolone sodium succinate should be given intravenously 1 hour before chemotherapy, at the beginning and end of chemotherapy for at least 5 minutes.

Chlorinated phenothiazine can be used with the first dose of methylprednisolone sodium succinate for increased effect. Severe emetogenic chemotherapy: 250 mg of methylprednisolone sodium succinate should be given alone, at the beginning and at the end of chemotherapy, with appropriate doses of metoclopramide or butyrofenone 1 hour before chemotherapy intravenously for at least 5 minutes.

Acute spinal cord injury: Treatment should be started within the first 8 hours of damage.

Patients who have started treatment within the first 3 hours of injury: IV bolus injection should be administered 30 mg/kg for 15 minutes, a 45-minute break should be given, and IV infusion for 23 hours should be given 5.4 mg/kg/hour.

Patients who started treatment within 3 to 8 hours of injury: IV bolus injection should be administered 30 mg/kg for 15 minutes, a break of 45 minutes should be given, and IV infusion for 47 hours should be given 5.4 mg/kg/hour.

There should be separate intravenous sites for infusion pumps. Treatment should be started within the first 8 hours of damage.

Pneumocystis carinii pneumonia in AIDS patients: Different dosing was used. According to one approach, 40 mg of methylprednisolone sodium succinate should be administered in gradually decreasing doses every 6 to 12 hours until a maximum of 21 days or until the end of pneumocystis therapy. Treatment should be started within 72 hours of anti-pneumocystis treatment.

Anaphylactic reactions: Firstly, adrenaline or noradrenaline should be applied for sudden hemodynamic effect and then PREDNOL-L should be injected intravenously with other accepted applications.

Hypersensitivity reactions: PREDNOL-L provides relief in 30 minutes to 2 hours. PREDNOL-L can be given to patients with asthma at a dose of 40 mg intravenously, and can be repeated

according to the patient's response. In some asthmatic patients, it may be advantageous to administer as a slow intravenous drip for several hours.

Graft rejection reactions after transplantation: The daily dose may need to be increased up to 1 g. Although the dose and protocol may vary in studies using methylprednisolone sodium succinate in the treatment of graft rejection reactions, published literature supports doses at this level (500 mg-1 g commonly used for acute rejection). Generally, high dose corticosteroid therapy should be applied until the patient is stable and should never exceed 48-72 hours depending on the patient's condition.

Cerebral edema: Corticosteroids are used to reduce or prevent cerebral edema associated with brain tumors.

It is important to decrease the corticosteroid dose gradually in patients with tumor-related edema in order to prevent rebound increase in intracranial pressure. If swelling appears in the brain as the dose decreases, it is resumed with higher and more frequent doses given parenterally.

Recommended dosage applications for edema due to brain tumor are as follows:

Administration A (1)	**Dose (mg)**	**Route of administration**	**Interval (hour)**	**Administration time**
Pre-operative	20	IM	3-6	
During operation	20-40	IV	1	
After the operation	20	IM	3	24 hour
	16	IM	3	24 hour
	12	IM	3	24 hour
	8	IM	3	24 hour
	4	IM	3	24 hour
	4	IM	6	24 hour
	4	IM	12	24 hour

Administration B (2)	**Dose (mg)**	**Route of administration**	**Interval (hour)**	**Administration time**
Pre-operative	40	IM	6	2-3
After the operation	40	IM	6	3-5
	20	Oral	6	1
	12	Oral	6	1
	8	Oral	8	1
	4	Oral	12	1
	4	Oral		1

Treatment should be discontinued after 10 days.

In other indications, the initial dose ranges from 10-500 mg. High doses are used for short-term treatment of serious, acute conditions. Initial doses up to 250 mg should be

administered intravenously for at least 5 minutes, and doses above 250 mg for at least 30 minutes. It should not be less than 0.5 mg / kg every 24 hours. Ongoing doses can be administered intravenously or intramuscularly at intervals determined based on the patient's response and clinical condition. Corticosteroid therapy is not a substitute for conventional therapy, but an adjunct therapy to conventional therapy.

Method of Administration:

After the ampoule containing lyophilized powder is dissolved with its solvent, the prepared solution can be applied by IM injection or IV infusion. In emergency situations, the preferred route of administration is IV injection. The desired dose is given slowly (over several minutes) by IV route. Intramuscular injections should be deep.

Additional information on special populations:

Kidney/Liver failure:

PREDNOL-L should be used under control in patients with kidney and liver failure.

In lupus nephritis: High dose general treatment, IV administration: 1 g daily is given for 3 days.

Pediatric population:

Doses from 30 mg/kg/day up to a maximum of 1 g/day are recommended for high-dose treatments of indications such as hematological, rheumatic or renal conditions. This dose can be given by dividing it into three during the day or on the following days. In graft rejection reactions after transplantation, doses from 10-20 mg/kg/day up to 3 days up to a maximum of 1 g/day are recommended. In the treatment of asthma, 1-4 mg/kg/day dose is recommended for 1-3 days.

Since there is a risk of regression in growth with the use of PREDNOL-L, it should not be used unless there are compulsory reasons in children.

Geriatric population:

There is no specific application, but it should be taken into consideration that the undesirable effects of corticosteroids may occur more seriously when planning treatment in geriatric patients and patients should be followed up clinically.

4.3. Contraindications

- Patients who have hypersensitivity to methylprednisolone, other glucocorticoids or any of the excipients in the formulation,
- Patients who have systemic fungal infection,
- It should not be used in patients with systemic infection without a specific anti-infective treatment.
- Intrathecal administration is contraindicated.
- Contraindicated in patients with known or suspected allergy to cow milk (see section 4.4).

4.4. Special use warnings and precautions

Undesirable effects should be minimized by using the lowest effective dose in a minimum time.

During long-term steroid therapy, adrenal cortical atrophy may develop and continue for many years even after discontinuation of treatment. The drug should not be stopped abruptly in patients who use systemic corticosteroids in doses higher than the physiological doses (about 6 mg of methylprednisolone) for more than 3 weeks. How to reduce during the dose reduction, varies widely, depending on the risk of relapse of the disease. Disease activity should be monitored during drug cessation. Systemic corticosteroid dose can be rapidly reduced to physiological doses if there is a low probability of relapse, but there is suspicion of suppression of the hypothalamus-pituitary-adrenal (HPA) during the drug cessation. When a daily dose of 6 mg of methylprednisolone is reached, the dose reduction rate is slowed to allow the HPA axis to recover.

In patients using systemic corticosteroids for up to 3 weeks, the drug may be stopped abruptly if the probability of disease relapse is low. In the vast majority of patients, use of corticosteroids at doses of 32 mg of methylprednisolone daily for up to 3 weeks is not expected to cause HPA-axis suppression. In the following patient groups, it is recommended to stop the drug gradually, even if the treatment period is 3 weeks or less:

- Patients who received repeated systemic corticosteroid cures (especially if it lasted longer than 3 weeks),
- After long-term (months or years) corticosteroid treatment, if a short-term cure was required within one year,
- Patients at risk of adrenocortical insufficiency other than exogenous corticosteroid treatment,
- Patients treated at doses higher than 32 mg methylprednisolone per day
- Patients receiving their doses in the afternoon repeatedly.

Patients should carry “Steroid Therapy” cards that clearly explain the dose of the drug and the duration of the treatment and explain the measures to be taken to minimize risks.

Cardiac arrhythmia, circulation collapse, cardiac arrest several cases have been reported following repeated high dose i.v. PREDNOL-L (more than 0.5 g over a period of less than 10 minutes). Bradycardia has been reported during and after high doses, regardless of infusion rate or duration.

Suppression of the inflammatory response and immune function increases infection sensitivity and severity. The clinical picture is often atypical; serious infections such as septicemia and tuberculosis can be masked and reach advanced stages before diagnosis. During drug administration new infections may develop.

Although chickenpox infection is normally a mild disease, it can be fatal in immunosuppressed patients. Patients (or parents) who have not previously had chickenpox should avoid contact with the people who have chickenpox or herpes zoster infection, seek immediate medical attention if contact occurs. Passive immunization with varicella zoster immunoglobulin (VZIG) should be considered for those who were in contact. People who take systemic corticosteroids or used it within 3 months and who are not immune to this disease are recommended to be vaccinated within 10 days after contact. If the diagnosis of chickenpox is confirmed, emergent treatment and specialist care is required. Corticosteroids won’t be stopped, even the dose may need to be increased.

Patients should be informed about avoiding measles and seeking immediate medical attention in the case of contact. Intramuscular prophylaxis may be needed with normal immunoglobulin.

Live vaccines should not be administered to immunosuppressive people. Although dead or toxoid vaccines can be given, their effects may be low.

The use of corticosteroids in active tuberculosis can only be used in conjunction with the systemic antituberculosis regimen in fulminant or disseminated tuberculosis. If corticosteroids should be used in patients with latent tuberculosis or tuberculin reactivity, close monitoring is required as the disease may be reactive. Chemoprophylaxis should be applied in patients requiring long-term corticosteroid therapy.

Anaphylactoid reactions have been reported rarely with parenteral therapy. Appropriate preventive measures should be taken before administration of the drug, especially in patients with a history of drug allergy.

It should be used with caution in patients taking cardioactive drugs such as digoxin due to steroid-induced electrolyte disturbance/potassium loss.

As it may cause more harm than benefits, corticosteroids should not be used in the treatment of head trauma and stroke.

Special care is required in the use of systemic corticosteroids in the following situations and patients should be monitored frequently:

- Osteoporosis (especially postmenopausal women are at risk).
- Hypertension or congestive heart failure.
- Existing or previous severe affective disorders (especially a history of steroid psychosis in the past).
- Diabetes mellitus (or family history for diabetes) (In diabetics, the metabolism status should be checked and, if necessary, the antidiabetic treatment should be readjusted.).
- Previous tuberculosis history or typical appearance in the chest film.
- Blurred vision or glaucoma (or family history of glaucoma).
- A history of myopathy with corticosteroids.
- Liver failure or cirrhosis.
- Kidney failure
- Epilepsy
- Peptic ulcer (Before starting Prednisolone treatment, it should be determined whether the patient has gastrointestinal ulcer and the dose to be applied should be determined individually.)
- Newly formed anastomosis in the intestine.
- Susceptibility to thrombophlebitis.
- Peritonitis.
- Abscess and other pyogenic infections.
- Ulcerative colitis.
- Diverticulitis.
- Myasthenia gravis (In patients with myasthenia gravis, especially using high doses of glucocorticoids, the disease may worsen and myasthenic crises can occur. Worsening usually occurs within the first two weeks after starting treatment. For this reason, the

initial dose for these patients should be low and gradually increased during the treatment.).

- Ocular herpes simplex, for the possibility of corneal perforation.
- Hypothyroidism.
- Recent myocardial infarction (myocardial rupture has been reported).

Especially after long-term treatment with high doses, sodium and fluid retention, hypokalemia tendency should be considered. In such cases, it is necessary to ensure adequate potassium intake, limit sodium intake and monitor serum potassium levels.

Kaposi's sarcoma has been reported in patients receiving corticosteroid therapy. Remission may occur with discontinuation of corticosteroid therapy.

Patients and/or their relatives should be warned about serious psychiatric adverse reactions that may occur with systemic corticosteroid therapy. Symptoms can appear within a few days to a few weeks after the start of treatment. After higher systemic exposure, this type of risk is greater. Although the vast majority of adverse reactions respond to dose reduction or drug discontinuation, specific treatment may be required. Patients and/or their relatives should be warned about seeking help, especially in the presence of symptoms such as depression or suicidal ideation. Warning should be made that in rare cases such reactions may also occur during dose reduction or within a short period after drug cessation as well as during drug treatment.

Particular attention should be paid to patients with a history of severe affective disorders in themselves or their first-degree relatives. These disorders include depressive or manic-depressive illness and previous steroid psychosis.

Immune System Effects

Cow's milk allergy

PREDNOL-L 40 mg contains bovine lactose monohydrate as an excipient and therefore may contain traces of cow's milk proteins (cow's milk allergens). In patients with cow's milk proteins allergy treated for acute allergic conditions, severe allergic reactions have been reported, including bronchospasm and anaphylaxis. PREDNOL-L 40 mg should not be administered to patients with known or suspected allergy to cow milk (see section 4.3).

For the treatment of acute allergic conditions, allergic reactions to cow's milk proteins should be considered in patients who take 40 mg of PREDNOL-L and whose symptoms worsen or who develop new allergic symptoms (see section 4.3). Use of PREDNOL-L 40 mg should be stopped and the patient's condition should be treated appropriately.

Use in children

Especially during any long-term prednisolone treatment that is applied to children, these patients should be carefully monitored for growth and development. Corticosteroids can cause growth retardation in infancy, childhood and adolescence, and this effect may not be reversible. Treatment should be limited to the lowest possible dose and the shortest duration to minimize suppression of the hypothalamus-pituitary-adrenal (HPA) axis and to minimize growth retardation.

Use in the elderly

With increasing age, side effects of systemic corticosteroids, especially osteoporosis, hypertension, hypokalemia, diabetes, susceptibility to infection, and skin thinning may occur more severely. Close clinical monitoring is necessary to avoid life-threatening reactions.

PREDNOL-L contains less than 1 mmol (23 mg) sodium per dose (40 mg); so it can be considered that it does not actually contain sodium.

PREDNOL-L contains 10 mg lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction

Digital glycosides: The effect of glycosides may increase due to potential hypokalemia.

Antihypertensive and diuretics: Corticosteroids can antagonize the desired effects of antihypertensive and diuretics.

Hypokalemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone may increase.

Antidiabetic agents: The effect of lowering blood sugar may decrease.

Coumarin derivatives: Anticoagulant effect may be alleviated.

Drugs that induce liver enzymes such as rifampicin, rifabutin, carbamazepine, aminoglutetimide, phenytoin and barbiturates: The corticosteroid effect may decrease.

Medicines that inhibit the CYP3A4 enzyme such as cimetidine, erythromycin, ketoconazole, itraconazole, diltiazem, and mibefradil: The metabolic rate of corticosteriods may decrease and serum concentration may increase.

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

Non-depolarizing muscle relaxants: The relaxant effect may be prolonged.

Estrogens (for example, contraceptive products): The need for corticosteroids may decrease. With the use of estrogens, the metabolism of corticosteroids, including methylprednisolone, may be impaired.

Nonsteroidal anti-inflammatory drugs (e.g. acetylsalicylic acid, indomethacin): The risk of gastrointestinal bleeding increases.

The clearance of salicylates increases with corticosteroids, which can cause salicylate toxicity. Caution should be paid if salicylates and nonsteroidal anti-inflammatory drugs are to be used with corticosteroids in patients with hypothrombinemia.

Cyclosporine: Mutual metabolism inhibition; the risk of cerebral convulsions increases.

Skin tests: Reactions to skin tests may be suppressed.

Vaccines: The response to toxoid and live or inactivated vaccines may decrease due to the inhibition of antibody response in patients receiving long-term corticosteroid therapy.

Corticosteroids can also increase the replication of some organisms found in live attenuated vaccines.

If possible vaccination or toxicoid administration should be delayed until discontinuation of corticosteroid treatment.

Alcohol/Nutrition/Herb interactions:

Alcohol: Use with alcohol should be avoided (may increase gastric mucosal irritation).

Food: Methylprednisolone inhibits calcium absorption. Caffeine should be restricted.

Herbal products: St. John's Wort can lower methylprednisolone levels. Concomitant use of with Cat’s claw and Echinacea should be avoided (they have immuno-stimulating effects).

4.6. Pregnancy and Lactation

General advice:

Pregnancy category: C

Women with childbearing potential/Contraception (Contraception):

In some case reports, contraception has been reported to decrease with treatment with conticosteroids in women using intrauterine devices.

Pregnancy period:

Methylprednisolone crosses the placental barrier. Administration of corticosteroids to pregnant animals can cause fetal development anomalies including cleft palate, retardation in intrauterine development, and effects on brain growth and development. There is no data showing that corticosteroids cause an increase in the frequency of congenital anomalies in human, but corticosteroids may increase the risk of intrauterine growth retardation in long-term or repeated use during pregnancy. There is only limited experience with the use and reliability of methylprednisolone in pregnancy. For this reason, PREDNOL-L should only be used during pregnancy or in cases where pregnancy cannot be prevented if there is a definite medical need.

Lactation period:

Methylprednisolone passes into breast milk in low amounts. The use of up to 40 mg daily methylprednisolone does not cause systemic effects in the baby. If high doses are required for clinical reasons, breastfeeding should be avoided to prevent the baby from taking methylprednisolone with breast milk.

Reproductive ability/Fertility:

Steroids can cause an increase or decrease in sperm count and mobility in some patients.

4.7. Effects on the ability to drive and use machines

Some undesirable effects (like decreased vision due to blurred vision or increased intraocular pressure, dizziness, headache) may impair the patient's concentration and reaction ability. Therefore, it may pose a risk for car or machine use.

4.8 Undesirable effects

Adverse events are listed according to system organ class and frequency with the following approach:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), unknown (cannot be estimated from the available data).

Infections and infestations

Unknown: Increased susceptibility to infections and severity of infections, masking serious signs of infection, opportunistic infections, recurrence of latent tuberculosis.

Blood and lymphatic system disorders

Unknown: Leukocytosis, thromboembolism.

Immune system diseases

Unknown: Hypersensitivity reactions including anaphylaxis, bronchospasm.

Endocrine diseases

Unknown: Suppression of the hypothalamus-pituitary-adrenal axis, suppression of growth in infants, children and adolescents, menstrual irregularity, amenorrhea. Cushingoid face (face in the moon), hirsutism.

Metabolism and nutritional diseases

Unknown: Sodium and water retention, potassium loss, hypotension or hypertension, hypokalemic alkalosis, congestive heart failure in sensitive patients, weight gain, impaired carbohydrate tolerance, increasing the need for antidiabetic therapy, negative nitrogen and calcium balance, increased appetite.

Psychiatric Diseases

Common: A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed, and labile mood psychological dependence and suicidal thoughts), psychotic reactions (including exacerbation of mania, delusion, hallucination, and schizophrenia), behavioral disorders, irritability, anxiety, sleep disorders, seizures, and cognitive function disorders including confusion and amnesia for all corticosteroids.

Psychological effects have been reported during withdrawing corticosteroids, the frequency is unknown. It has been reported that intracranial pressure increases (pseudotumor cerebri) with papilloedema in children, usually after withdrawal of methylprednisolone therapy.

Eye diseases

Unknown: increased intra-ocular pressure, glaucoma, papilloedema with possible damage to the optic nerve, cataract, corneal and scleral thinning, exacerbation of ophthalmic viral or fungal disease.

Cardiac diseases

Unknown: Myocardial rupture following myocardial infarction, cardiac arrest, cardiac arrhythmia.

Gastrointestinal diseases

Unknown: Dyspepsia, peptic ulcer with perforation and hemorrhage, abdominal distension, esophageal ulcer, esophageal candidiasis, acute pancreatitis, perforation of the bowel, gastric hemorrhage. Especially with rapid application, nausea, vomiting and bad taste can be seen in the mouth.

Following corticosteroid therapy, increased alanine transaminase (ALT, SGPT), increased aspartate transaminase (AST, SGOT) and increased alkaline phosphatase were observed. These changes are usually minor and not related to clinical syndrome; reversal when the treatment is stopped.

Skin and subcutaneous diseases

Unknown: Impaired repair, petechiae, ecchymosis, skin atrophy, bruising, cracked skin, telangiectasia, acne, hypopigmentation or hyperpigmentation. Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Musculoskeletal and Connective Tissue Disorders

Unknown: Proximal myopathy, osteoporosis, spine and long bone fractures, avascular osteonecrosis, tendon rupture.

General disorders and diseases related to the administration site

Unknown: Hiccup

Withdrawal symptoms: Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is mostly the case in continuous treatment.

Withdrawal syndrome may also occur including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. Reporting allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals should report any suspected adverse reaction to Turkey Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9 Overdose and Treatment

There is no clinical syndrome of acute over dosage with PREDNOL-L. Treatment should be symptomatic and supportive. Methylprednisolone is dialyzable. Following the chronic overdose, the dose should be gradually reduced against the possibility of adrenal suppression risk. In this case, the patient may need to be supported during another stress attack.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids

ATC Code: H02AB04

Methylprednisolone is a synthetic and fluorine-free corticosteroid. The anti-inflammatory effect of methylprednisolone is stronger than that of prednisolone. Its inducing effect on water and salt retention in the body is less than that of prednisolone.

Methylpredniolone sodium succinate has the same metabolic and anti-imflammatory 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 succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This data is consistent with the relative potency of methylprednisolone and hydrocortisone after oral administration.

Glucocorticoids have a strong and diverse metabolic effect. In addition, they alleviate the body's immune response to different stimuli.

Although natural corticosteroids (hydrocortisone and cortisone) have salt-retaining properties, they are used for replacement therapy in case of adrenocortical insufficiency. Synthetic analogues of natural corticosteroids are used in many organ system disorders due to their strong anti-inflammatory activities.

5.2 Pharmacokinetic properties

General properties

Absorption:

After an intravenous infusion of Methylprednisolone, 30mg/kg over a 20 minute period or 1g over 30 to 60 minutes, peak methylprednisolone plasma concentrations of approximately 20µg/ml were achieved. Peak methylprednisolone levels of 42-47µg/100ml were reported following a single 40mg IV bolus injection to six 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. Peak methylprednisolone plasma levels of 33.67 µg/100ml were achieved in two hours after a single 40 mg IM injection to 22 adult male volunteers.

Distribution:

Methylprednisolone is extensively bound to plasma proteins, mainly to globulin. Methylprednisolone is widely distributed throughout the body by a two-compartment model. The mean volume of distribution was reported to be between 41-61.5 L in thirty-four adult volunteers.

Biotransformation:

Methylprednisolone is metabolized in the liver to inactive metabolites, the major ones being 20β-hydroxymethylprednisone and 20 alfa-hydroxy-6a-methylprednisone.

Elimination:

Total body clearance following intravenous or intramuscular injection of methylprednisolone to healthy adult volunteers is approximately 15 – 16l/hr. Methylprednisolone is excreted mainly from the kidneys. Methylprednisolone is excreted in the urine in the form of inactive metabolites. The mean elimination half-life ranges between 2.4-3.5 hours in normal healthy adults and regardless of the route of administration.

5.3 Preclinical safety data

Adequate studies for carcinogenic or mutagenic potential of corticosteroids have not been performed in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilized ampoule

Sodium phosphate dibasic anhydride

Lactose monohydrate (made from cow's milk)

Sodium chloride

6.2 Incompatibilities

Perfusion should be done in isotonic solutions (saline or glucose).

6.3 Shelf life

60 months

It should be immediately used after reconstitution.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

PREDNOL-L 40 mg lyophilized injection ampoule is supplied with 1 colorless Type I glass ampoule containing white lyophilized powder together with 1 colorless Type I glass ampoule containing 2 ml of water for injection in a carton box.

6.6 Special precautions for disposal and other handling

It must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORIZATION HOLDER

Gensenta İlaç Sanayi ve Ticaret A.Ş.
İş Kuleleri, Levent Mah., Meltem Sok. No: 10 Kule: 2 Kat: 24
4. Levent, Beşiktaş, Istanbul
Phone: 0212 337 38 00

8. MARKETING AUTHORIZATION NUMBER

117/70

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORISATION

First authorization date: 15.01.1974

Authorization renewal date: 02.11.2006

10. DATE OF RENEWAL OF SPC

04.09.2018