

PRODUCT MONOGRAPH

Pr PEDIAPRED[®]

ORAL LIQUID

(Prednisolone Sodium Phosphate)

(equivalent to 5 mg/5 mL prednisolone)

GLUCOCORTICOID/ANTI-INFLAMMATORY

sanofi-aventis Canada Inc.
2905 Place Louis-R.-Renaud
Laval, Quebec H7V 0A3

Date of Revision:
May 25, 2018

Submission Control No.: 212653

s-a Version 5.0 dated May 25, 2018

PRODUCT MONOGRAPH

NAME OF DRUG

PEDIAPRED[®]

ORAL LIQUID

(Prednisolone Sodium Phosphate)
(equivalent to 5 mg/5 mL prednisolone)

THERAPEUTIC CLASSIFICATION

Glucocorticoid/Anti-inflammatory

ACTIONS AND CLINICAL PHARMACOLOGY

PEDIAPRED[®] (prednisolone sodium phosphate) is a synthetic adrenocortical steroid derivative with predominantly glucocorticoid properties possessing anti-inflammatory and immunosuppressive action.

Prednisolone sodium phosphate belongs to the pharmacologic class of glucocorticoid / anti-inflammatory drugs which, following systemic absorption, diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes may enter the cell nucleus, bind to DNA and stimulate transcription of mRNA. Subsequent cellular responses result in a variety of local and systemic effects. Inflammatory processes such as edema, fibrin deposition, decreased prostaglandin/thromboxane synthesis, capillary dilatation, migration of leukocytes, the phagocytosis stage of wound healing and cicatrization are inhibited. Immune reactions are suppressed. Metabolically, protein catabolism and increased gluconeogenesis, along with decreased peripheral utilization of glucose, leads to glycogen storage in the liver, increased blood glucose concentration and insulin resistance (diabetogenic effect). During therapy lipolysis is enhanced and abnormal distribution of fat may result (Cushingoid effect). Skeletal calcium is mobilized and lost via renal excretion. Glucocorticoids, in general, augment renal glomerular filtration and promote urate excretion.

In respect of electrolyte and water balance, sodium tends to be reabsorbed and potassium and hydrogen excreted resulting in water retention and risk of hypokalemic alkalosis.

Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration. PEDIAPRED Oral Liquid produces a 20% higher peak plasma level of prednisolone which occurs approximately 15 minutes earlier than that seen with tablet

formulations. Prednisolone is 70-90% protein-bound in the plasma and it is eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolized mainly in the liver and excreted in the urine as sulphate and glucuronide conjugates.

INDICATIONS AND CLINICAL USE

Management of conditions known to be responsive to PREDNISONE or PREDNISOLONE where anti-inflammatory action or immunosuppression or adrenocortical supplementation and replacement is required.

For most indications, glucocorticoid administration provides symptomatic relief, but has no effect on the underlying disease processes. Use of these medications does not eliminate the need for other therapies that may be required.

PEDIAPRED is appropriate for pediatric usage and for those patients with difficulty swallowing solid oral dosage forms.

CONTRAINDICATIONS

PEDIAPRED is contraindicated in patients with:

- Untreated systemic fungal infections.
- Known hypersensitivity to prednisone or prednisolone or any of the excipients in the liquid (see PHARMACEUTICAL INFORMATION, Composition).
- Chicken pox, measles, or uncontrolled active infections

WARNINGS

Endocrine and Metabolism

Glucocorticoid-induced suppression of HPA (Hypothalamic-Pituitary-Adrenal) function is dependent on dose and duration of treatment. Recovery occurs gradually as the steroid dose is reduced and withdrawn. Suppression persists for a period of time after withdrawal depending on dose and length of treatment time.

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

Average and large doses of corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Pheochromocytoma crisis, which can be fatal, has been reported after administration of corticosteroids. Corticosteroids should only be administered to patients with suspected or identified pheochromocytoma after an appropriate risk/benefit evaluation.

Immune

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

If corticosteroids have to be used in the presence of fungal or bacterial infections, institute appropriate anti-infective therapy.

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

While on corticosteroid therapy, patients should not be vaccinated against measles. **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 lack of antibody response.**

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles can have a more serious or even fatal course in non-immune children or adults who have not had these diseases, and particular care should be taken to avoid exposure. It is not known whether the risk of developing serious cases of these infections is due to prior corticosteroid treatment, or to the contribution of the underlying disease which is being treated. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

The use of PEDIAPRED is contraindicated in patients with chicken pox, measles or uncontrolled active infections (see CONTRAINDICATIONS).

Ophthalmologic

Prolonged use of corticosteroids may produce posterior subcapsular cataracts or glaucoma with possible damage to the optic nerves and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Systemic glucocorticoid treatment can cause chorioretinopathy which can lead to visual disorders including visual loss. Prolonged use of systemic glucocorticoid treatment even at low dose can cause chorioretinopathy. If a patient under glucocorticoid treatment presents with visual disturbances, the patient should be considered for referral to an ophthalmologist for further evaluation.

PRECAUTIONS

During prolonged corticosteroid therapy, routine laboratory studies such as urinalysis, 2-hour postprandial blood sugar determinations, blood pressure monitoring, body weight and chest X-ray should be performed at regular intervals. If doses of prednisolone are high, serum potassium should be monitored regularly. Serious consideration of upper gastrointestinal studies should be contemplated when patients complain of gastric symptoms while on this medication. In general, prolonged therapy above 8 mg/day is associated with increased incidence of adverse effects; mental disorders are associated with doses exceeding 40 mg/day.

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstated. Since mineralocorticoid secretion may be impaired, salt and/or mineralocorticoid should be administered concurrently.

Pediatric Use

Hypertrophic cardiomyopathy has been reported after systemic administration of glucocorticosteroids in preterm infants. In infants receiving administration of systemic glucocorticosteroids, echocardiograms should be performed to monitor myocardial structure and function.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Administration of corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen.

Pediatric patients demonstrate greater susceptibility to corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients. HPA axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children taking oral corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches and bilateral papilloedema.

General Use

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis of the liver.

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

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Following prolonged therapy, psychological and/or physiological dependence may develop. Withdrawal of glucocorticoids may result in symptoms of the glucocorticoid withdrawal syndrome including: fever, myalgia, arthralgia and malaise. This may occur in patients even without evidence of adrenal insufficiency.

Aspirin (ASA) and other NSAIDs should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Corticosteroids should be used with caution in the following clinical conditions: non-specific ulcerative colitis (if there is a probability of impending perforation), abscess or other pyogenic infection, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, cardiac disease, thromboembolic disorders and diabetes mellitus.

In myasthenia gravis, hospitalization with careful observation is recommended because transient worsening of symptoms, possibly leading to respiratory distress, may precede clinical improvement.

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.

Patients should be warned not to discontinue the use of PEDIAPRED abruptly or without medical supervision, to advise any medical attendants that they are taking PEDIAPRED and to seek medical advice at once should they develop fever or other signs of infection (Refer to "Patient Information").

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay (See WARNINGS). The use of PEDIAPRED is contraindicated in patients with chicken pox, measles or uncontrolled active infections (see CONTRAINDICATIONS).

Steroids may increase or decrease motility and number of spermatozoa in some male patients. However, it is not known whether reproductive capacity in humans is adversely affected.

Carcinogenicity and Mutagenicity

Limited information is available. Glucocorticoids produce cleft palate in the offspring when administered to pregnant mice, rats and hamsters. There are few studies on the carcinogenicity or mutagenicity of prednisolone in animals.

Drug Interactions

Since prednisolone sodium phosphate is metabolized in the liver, the possibility exists that concomitant administration of other hepatically metabolized drugs may lead to interactions (e.g. barbiturates). Dosage adjustment may be required for hepatic CYP450 enzyme inducers and inhibitors.

It is recommended to increase the maintenance dose of glucocorticoids if the following drugs are administered at the same time: anticonvulsants (phenobarbital, phenytoin), certain antibiotics (rifampin), anticoagulants (coumarin) and bronchodilators (ephedrine). If the patient receiving glucocorticoids is treated at the same time with some other antibiotics (erythromycin), ketoconazole, estrogens or preparations containing estrogens, a reduction in the dose of prednisolone sodium phosphate is recommended.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, may increase the risk of systemic corticosteroid side-effects. The combination should be avoided unless the benefit outweighs the increased risk of such side-effects, in which case patients should be closely monitored

Anticholinesterase effects may be antagonized in myasthenia gravis. Toxicity may be enhanced when cyclosporin and glucocorticoids are combined in organ transplant patients.

Co-administration with digitalis glycosides may enhance the possibility of digitalis toxicity associated with hypocalcemia. Isoniazid and salicylate serum concentrations may be decreased upon co-administration with glucocorticoids.

Potassium-depleting agents (e.g. thiazide diuretics) may enhance hypocalcemia and hypokalemia secondary to glucocorticoid use. Co-administration with non-steroidal anti-inflammatories may increase the risk of gastrointestinal ulceration. Immunologic response to vaccines and toxoids is reduced by glucocorticoids which may also potentiate the replication of organisms in attenuated vaccines (e.g. measles). Glucocorticoids may alter laboratory or radiological tests for serum T₃ or serum protein-bound iodine, may decrease T₄ minimally or decrease the uptake of ¹³¹I iodine.

Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy (e.g. Addison's disease).

Pregnancy

Prednisolone sodium phosphate (corticosteroids) 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. PEDIAPRED should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone sodium phosphate 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.

Nursing Mothers

Prednisolone sodium phosphate is excreted in breast milk. Caution should be exercised when PEDIAPRED is administered to a nursing woman.

ADVERSE REACTIONS

Corticosteroids have a potential for multiple adverse effects. There are essentially two types of toxicity observed when administered in therapeutic dosages: withdrawal effects, which could produce life-threatening adrenal insufficiency, and high dosage over long periods, which could produce fluid/electrolyte disturbances, hyperglycemia, increased susceptibility to infections, peptic ulceration, osteoporosis, myopathy, behavioural disturbances, cataracts, or Cushing's habitus. Single doses, or short courses of therapy (over several days), are usually associated with less harmful effects. The approach to therapy should follow logical and rational sequence of: (i)

attempting to control the condition with more conventional mode(s) of management, (ii) weighing the benefits of steroid therapy against the risks, (iii) commencing therapy with high loading dose, reducing to the minimum effective dosage as soon as possible.

Cardiac Disorders

Hypertrophic cardiomyopathy in preterm infants.

Fluid and Electrolyte Disturbances

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

Musculoskeletal

Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones.

Gastrointestinal

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

Dermatologic

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

Metabolic

Negative nitrogen balance due to protein catabolism.

Neurological

Convulsions, increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, vertigo, headache.

Endocrine

Menstrual irregularities, development of cushingoid state, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness, suppression of growth in children, decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics; pheochromocytoma crisis.

Ophthalmic

Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos, blurred vision, chorioretinopathy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported.

Treatment of acute overdosage is by immediate gastric lavage or emesis. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage of prednisolone may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION

The initial dosage may vary from 5 to 60 mg prednisolone base per day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice, while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time there is a lack of satisfactory clinical response, PEDIAPRED should be discontinued and the patient transferred to other appropriate therapy. **IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT.** Standardized dosing is not available for oral corticosteroids. Therefore, any adjustments in consideration of age or renal function of the patient should be taken into account, along with the patient's weight and severity of the disease when the initial dosage is established. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements, at appropriate time intervals, until the lowest dosage, which will maintain an adequate clinical response, is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation, it may be necessary to increase the dosage of prednisolone for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually, rather than abruptly, to avoid glucocorticoid withdrawal syndrome.

If on a once-daily therapy, PEDIAPRED should be administered in the morning to simulate the natural circadian rhythm of corticosteroid secretion.

EQUIVALENT MILLIGRAM DOSAGE OF GLUCOCORTICOIDS^{1,2}

NAME	MG/DOSE
Cortisone	25
Hydrocortisone	20
Prednisolone	5
Prednisone	5
Methylprednisolone	4
Triamcinolone	4
Paramethasone	2
Betamethasone	0.6
Dexamethasone	0.75

1. These dose relationships apply only to oral or intravenous administration of these compounds.
2. When these substances or their derivatives are injected intra-muscularly into joint spaces, their relative properties may be greatly altered.

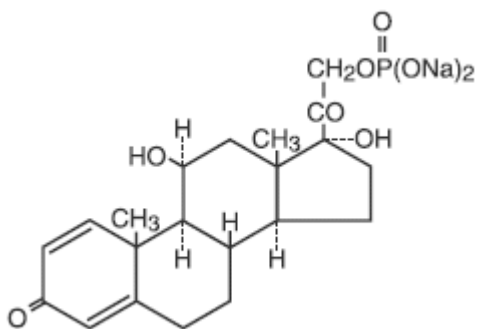
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Prednisolone sodium phosphate

Chemical Name: pregna-1, 4 diene-3, 20-dione, 11, 17-dihydroxy-21-(phosphonoxy)-, disodium salt, (11 β)-

Structural Formula:



Molecular Formula: C₂₁H₂₇Na₂O₈P

Molecular Weight: 484.39

Description: White or slightly yellow friable granules or powder, freely soluble in water, soluble in methanol, slightly soluble in alcohol and chloroform, very slightly soluble acetone and in dioxane.

Composition:

PEDIAPRED - Medicinal Ingredient: Each 5 mL of PEDIAPRED Oral Liquid contains prednisolone sodium phosphate (equivalent to 5 mg/5 mL prednisolone).

Nonmedicinal Ingredients: Dibasic sodium phosphate, edetate disodium, methylparaben, purified water, sodium phosphate monobasic, sorbitol, artificial raspberry flavor.

Stability and Storage Recommendations:

Store at 15-30°C. Do not refrigerate. Keep bottle tightly closed.

AVAILABILITY AND DOSAGE FORMS

PEDIAPRED Oral Liquid is a dye-free, colourless to, slightly yellow raspberry-flavored solution supplied in 120 mL bottles. Each 5 mL (teaspoonful) contains 5.0 mg prednisolone base (as prednisolone sodium phosphate) in a palatable, aqueous vehicle.

PATIENT INFORMATION

DESCRIPTION OF MEDICATION

PEDIAPRED is the proprietary name of sanofi-aventis Canada Inc. for prednisolone oral liquid (as prednisolone sodium phosphate). PEDIAPRED contains 1 mg/mL of prednisolone base.

The nonmedicinal ingredients in PEDIAPRED are: artificial raspberry flavor, dibasic sodium phosphate, edetate disodium, methylparaben, purified water, sodium phosphate monobasic, sorbitol.

Prednisolone is an adrenocorticoid, which belongs to the general family of medicines called steroids. There are many uses for this type of product: it may help replace those normally produced by your body, or it may be useful to provide relief from inflammation or allergic reactions which accompany a large number of different diseases such as skin problems, asthma or arthritis. It may also be given to you by your doctor as part of a treatment for your particular problem.

PEDIAPRED is available only with your physician's prescription.

BEFORE USING THIS MEDICATION

You should inform your physician if any of the following apply to you:

- You have already taken PEDIAPRED or any other corticosteroids and developed an allergy or intolerance to any of them. Also, tell your physician if you are allergic to any other substances such as foods, preservatives or dyes.
- You are pregnant, intend to become pregnant, or are breast feeding, or intend to breast-feed.
- You are taking other medication, especially antacids, barbiturates, carbamazepine, phenytoin, antidiabetics (oral or insulin), digitalis, diuretics or medicine containing potassium or sodium.
- You suffer from other medical problems especially AIDS, systemic infections (such as chicken pox, measles, or other infections) or local infections, stomach or intestine problems, bone disease, diabetes, heart disease, high blood pressure, kidney disease or kidney stones, myasthenia gravis, recent surgery or serious injury or if you are going to have skin test injections.

While you are being treated with this medication, and even after you have stopped taking it, do not have any immunizations without your doctor's approval. Also, other people living in your home should not receive oral polio vaccine, since there is a chance they could pass the polio virus on to you.

PROPER USE OF THIS MEDICATION

PEDIAPRED is a potent medicine and it is very important that you follow your doctor's directions on how to use it. Do not use more or less of it than you are supposed to. Do not take it more or less often than you are supposed to, and do not continue to use it for longer periods than you are supposed to.

Do not stop using PEDIAPRED without your doctor's approval. In many cases, PEDIAPRED must be gradually reduced before stopping completely, or serious side effects can occur.

Stomach problems may be more likely to occur if you drink alcoholic beverages while being treated with this medication.

Your physician will monitor your clinical condition and may ask for blood tests at regular intervals. It is important to attend these visits because your doctor may want to change the dosage and ensure there are no unwanted effects occurring.

Notify your physician about any illness which may develop during your treatment with PEDIAPRED and about any new prescription or non-prescription medication you may take. If you require medical help for other reasons, inform the attending physician that you are taking PEDIAPRED.

Take this medicine with food to help prevent stomach upset. If stomach upset, burning, or pain continues, check with your doctor.

Missed Doses

If you miss a dose of this medicine and your suggested dosing schedule is:

One dose every other day -- Take the missed dose as soon as possible if you remember it the same morning, then go back to your regular dosing schedule. If you do not remember the missed dose until later, wait and take it the following morning. Then skip a day and start your regular dosing schedule again.

One dose a day -- Take the missed dose as soon as possible, then go back to your regular dosing schedule. If you do not remember until the next day, skip the missed dose and do not double the next one.

Several doses a day -- Take the missed dose as soon as possible, then go back to your regular dosing schedule. If you do not remember until your next dose is due, double the next dose.

If you have any questions about this, check with your physician or pharmacist.

Notify your physician if you suffer any side effects (see next section).

Storage Information

Store at 15 -30°C. Do not refrigerate. Keep bottle tightly closed.

This medicine is prescribed for your specific medical problem and for your own use only. **Do not give it to other people.**

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

SIDE EFFECTS OF THIS MEDICATION

PEDIAPRED may cause some unwanted side effects. Usually these do not occur if you are taking the medication for a short period; however, if you do experience one of the following after a short period of using PEDIAPRED, contact your doctor: decreased or blurred vision, frequent urination, increased thirst, skin rash.

If you are taking PEDIAPRED, consult your doctor if any of the following occur: acne or other skin problems, back or rib pain, bloody or black tarry stools, filling or rounding of the face, irregular heartbeats, menstrual problems, depression, mood or mental changes, muscle cramps or pains or weakness, nausea or vomiting, if you see halos around lights, sore throat and fever, continued stomach pain or burning, swelling of feet or lower legs, unusual tiredness or weakness, wounds that will not heal, high blood pressure, rapid heartbeat, heavy sweating, headache, changes in vision.

Other side effects may occur which usually go away during treatment: indigestion, increased appetite, nervousness or restlessness, trouble sleeping or weight gain. If these symptoms persist, contact your doctor.

After you stop taking PEDIAPRED, especially if you have been taking it or similar medication to it for a long time, your body may need time to adjust. During this time, you should contact your doctor if you experience any of the following symptoms: pain in the abdomen, stomach or back, dizziness or fainting, fever, loss of appetite, muscle or joint pain, nausea or vomiting, shortness of breath, unusual tiredness or weakness, unusual weight loss.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

IF YOU NEED ANY FURTHER INFORMATION, ASK YOUR PHYSICIAN OR PHARMACIST.

PHARMACOLOGY

Prednisolone sodium phosphate is a synthetic corticosteroid with, primarily, glucocorticoid activity. Its primary actions are via control of protein synthesis, eliciting specific effects within given metabolic systems. Corticosteroids generally act by (i) conversion of protein to carbohydrate, protecting glucose-dependent cerebral functions by stimulating glucose formation; (ii) decreasing glucose utilization in peripheral tissue and increasing hepatic glycogen storage; (iii) promoting gluconeogenesis by peripheral and hepatic activity, protein catabolism for amino acid mobilization as substrate for glucose/glycogen production.

Glucocorticoids have only slight mineralocorticoid activity; however prednisolone can promote sodium influx and potassium efflux across cell membranes, and decreases calcium absorption by the gastrointestinal tract. Although not thought to be related to electrolyte imbalance, prednisolone, during prolonged therapy, may result in hypertension due to unclear etiology. Decreased bone formation, and increased resorption do occur as a result of decreased calcium absorption which decreases plasma calcium levels, increasing PTH secretion and osteoclast activity.

Excessive amounts of glucocorticoids such as prednisolone causes skeletal muscle wasting. The mechanism for this is not known.

The effects on the Central Nervous System are varied - mood elevation, euphoria, insomnia; this may be due to an increase in brain excitability unrelated to sodium or potassium levels.

Glucocorticoids increase the hemoglobin and red cell content of blood, and retard erythrophagocytosis. They increase the number of polymorphonuclear leukocytes, decrease lymphocytes, eosinophils and monocytes. T-lymphocytes are depressed more than β -lymphocytes.

Glucocorticoids prevent or suppress tissue response to the inflammatory process, and reduce the symptoms of inflammation without affecting the underlying cause. Their action is via the inhibition of neutrophil, leukocyte, monocyte-macrophage accumulation at the site of inflammation. Glucocorticoids are effective in the prevention and suppression of cell-mediated (delayed hypersensitivity) immune reactions which may occur via similar mechanisms, as described for anti-inflammatory activity.

Prednisolone is rapidly and almost completely absorbed following oral administration. It is reversibly bound (90%) with high affinity to corticosteroid binding globulin (Transcortin) or to albumin, with lower affinity, in plasma. Caution should be exercised in patients with decreased serum protein binding of steroids, as the free, or pharmacologically active, prednisolone levels can vary. Prednisolone is the active form; it is also the active metabolite of prednisone, which must be converted to prednisolone for biological activity. The pharmacokinetics of prednisolone are as follows:

% Availability (oral)	82 +/- 13
% Urinary Excretion	90 - 95
Clearance (mL.min ⁻¹ kg ⁻¹)	8.7 +/- 1.6
Volume of Dist. (L/kg)	1.5 +/- 0.2
T2 (hours)	2.2 +/- 0.1

Prednisolone is metabolized primarily by the liver and excretion is mainly renal.

For prednisolone, as other glucocorticoids, usage and dosage varies depending on the indication, the duration of treatment, and the reaction of the patient. In general, high doses are administered for short term therapy, and the lowest possible dose which provides adequate response is maintained for long term therapy. The daily dosage can range from 5 - 100 mg prednisolone.

Prednisolone is an extremely potent and effective agent, with the potential for multiple adverse effects. There are essentially 2 types of toxicity observed when administered in therapeutic dosages: withdrawal effects, which could produce life-threatening adrenal insufficiency; and high dosage over long periods, which could produce fluid/electrolyte disturbances, hyperglycemia, increased susceptibility to infections, peptic ulceration, osteoporosis, myopathy, behavioural disturbances, cataracts, or Cushings' habitus. Single doses, or short courses of therapy (over several days) are usually without harmful effects. The approach to institution of therapy should follow the sequence of: (i) attempting to control the condition with more conventional mode(s) of therapy; (ii) weighing the benefits of steroid therapy against the risks; (iii) commencing therapy with a high loading dose, reducing to the minimum effective dosage as soon as possible.

During prolonged therapy, routine laboratory studies such as urinalysis, 2-hour postprandial blood sugar determinations, body weight and chest X-ray should be performed at regular intervals. If doses of prednisolone are high, serum potassium should be monitored regularly. If the patient has a history of gastrointestinal (GI) disturbances, upper GI X-rays should be performed. Prolonged therapy above 8 mg/day is associated with increase rise of adverse effects; mental disorders are associated with doses exceeding 40 mg/day.

TOXICOLOGY

Limited information is available. Glucocorticoids produce cleft palate when administered to pregnant mice, rats and hamsters. There are few studies on the carcinogenicity or mutagenicity of prednisolone in animals.

SELECTED BIBLIOGRAPHY

1. Al-Habet SMH, Rogert HJ. Effect of food on the absorption and pharmacokinetics of prednisolone from enteric-coated tablets. *Eur J Clin Pharmacol* 1989; 37(4):423-6
2. Al-Habet SMH, Rogert HJ. Urinary excretion of prednisolone following intravenous administration in humans. *J Clin Pharmacol* 1989; 29(10):922-7
3. Bacon GE, Spencer ML. Pediatric Use of Steroids. *Med Clin North Am* 1973; 57(5):1265-76
4. Bergrem H, Opedal I. Bioavailability of prednisolone in patients with intestinal malabsorption; the importance of measuring serum protein-binding. *Scand J Gastroenterol* 1983; 18(4):545-9
5. Bergrem H, Grottum P, Rugstad HE. Pharmacokinetics and protein binding of prednisolone after oral and intravenous administration. *Eur J Clin Pharmacol* 1983; 24(3):415-9
6. Bergrem H, Ritland S, Opedal I, Bergan A. Prednisolone pharmacokinetics and protein-binding in patients with portosystemic shunt. *Scand J Gastroenterol* 1983; 18(2):273-6
7. Bergrem H, Jervell J, Flatmark A. Prednisolone pharmacokinetics in cushingoid and non-cushingoid kidney transplant patients. *Kidney Int* 1985; 27(2):459-64
8. Boekenoogen SJ, Szeffler SL, Jusko WJ. Prednisolone disposition and protein binding in oral contraceptive users. *J Clin Endocrinol Metab* 1983; 56(4):702-9
9. Buhner M, Frey FJ, Frey BM. Prednisolone concentrations in cerebrospinal fluid after different prednisolone prodrugs. *Br J Clin Pharmacol* 1991; 31(1):111-3
10. Conti M, Frey FJ, Escher G *et al.* Renal handling of prednisolone/prednisone: Effect of steroid dose and 11-beta-hydroxysteroid dehydrogenase. *Nephrology, Dialysis, Transplantation* 1994; 9(11):1622-8
11. Dawson KP, Sharpe C. A comparison of the acceptability of prednisolone tablets and prednisolone sodium phosphate solution in childhood acute asthma. *Aust J Hosp Pharmacy* 1993; 23(5):320-3
12. Deshpande A, McKenzie SA. Short course of steroids in home treatment of children with acute asthma. *Br Med J (Clin. Res.)*1986; 293(6540):169-71

13. De Silv M, Binder A, Hazleman BL. The timing of prednisolone dosage and its effect on morning stiffness in rheumatoid arthritis. *Ann Rheum Dis* 1984; 43(6):790-3
14. Dove AM, Szeffler SJ, Hill MR *et al.* Altered prednisolone pharmacokinetics in patients with cystic fibrosis. *J Ped* 1992; 120(5):789-94
15. Ferry JJ Jr, Wagner JG. The non-linear pharmacokinetics of prednisone and prednisolone. I. Theoretical Biopharm Drug Dispos 1986; 7(1):91-101
16. Frey BM, Frey FJ. The effect of altered prednisolone kinetics in patients with the nephrotic syndrome and in women taking oral contraceptive steroids on human mixed lymphocyte cultures. *J Clin Endocrinol Metab* 1985; 60(2):361-9
17. Frey BM, Schaad HJ, Frey FJ. Pharmacokinetic interaction of contraceptive steroids with prednisone and prednisolone. *Eur J Clin Pharmacol* 1984; 26(4):505-11
18. Frey BM, Seeberger M, Frey FJ. Pharmacokinetics of three prednisolone prodrugs. Evidence of therapeutic inequivalence in renal transplant patients with rejection. *Transplantation* 1985; 39(3):270-4
19. Frey FJ, Horber FF, Frey BM. Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. *Clin. Pharmacol. & Therapeutics* 1988; 44(5):510-21
20. Frey FJ, Frey BM. Altered plasma protein-binding of prednisolone in patients with the nephrotic syndrome. *Am J Kidney Dis* 1984; 3(5):339-48
21. Gambertoglio JG, Holford HG, Lizak PS *et al.* The absence of effect of azathioprine on prednisolone pharmacokinetics following maintenance prednisolone doses in kidney transplant patients. *Am J Kidney Dis* 1984; 3(6):425-9
22. Gambertoglio JG, Frey FJ, Holford NH *et al.* Prednisone and prednisolone bioavailability in renal transplant patients. *Kidney Int* 1982; 21(4):621-6
23. Garg V, Jusko WJ. Bioavailability and reversible metabolism of prednisone and prednisolone in man. *Biopharmaceutics & Drug Disposition* 1994; 15(2):163-172
24. Garg V, Jusko WJ. Simultaneous analysis of prednisone, prednisolone and their major hydroxylated metabolites in urine by high-performance liquid chromatography. *J Chromatography-Biomedical Applications* 1991; 567(1):39-47
25. Greenberger PA, Chow MJ, Atkinson AJ Jr. *et al.* Comparison of prednisolone kinetics in patients receiving daily or alternate-day prednisone for asthma. *Clin Pharmacol & Therapeutics* 1986; 39(2):163-8

26. Greenberger PA, Odeh YK, Frederiksen MC *et al.* Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol & Therapeutics* 1993; 53(3):324-8
27. Griffin PH, Salaman JR. Towards the Belfast immunosuppressive regimen: a prospective trial of low versus high dose steroids and once versus twice daily immunosuppression. *Br J Surg* 1985; 72(1):10-2
28. Gustavson LE, Legler UF, Benet LZ. Impairment of prednisolone disposition in women taking oral contraceptives or conjugated estrogens. *J Clin Endocrinol Metab* 1986; 62(1):234-7
29. Hayner RC, Murad F. Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogues, inhibitors of adrenocortical steroid biosyntheses. In: Gilman AG, Goodman LS, Rall TE, Murad F, eds. *The pharmacological Basis of Therapeutics*. MacMillian Publishing Company. 1985; 1459-89
30. Jick H. What to Expect from Prednisolone. *Drug Therapy* 1975; 85-90
31. Lam WK, So SY, Yu DY. Response to oral corticosteroids in chronic airflow obstruction. *Br J Dis Chest* 1983; 77(2):189-98
32. Legler UF, Benet LZ. Marked alterations in dose-dependent prednisolone kinetics in women taking oral contraceptives. *Clin Pharmacol Ther* 1986; 39(4):425-9
33. Mandal SK, Singhamahapatra AB, Goshdastidar A. Changes in brain cholesterol and its regional distribution under the influence of prednisolone. Department of Physiology, University College of Medicine, Calcutta University. *Indian J Physiol Pharmacol (INDIA)* 1985; 29(4):255-8
34. Marwah RJ, Pickup ME, Al-Shakarchi H *et al.* A pharmacological and clinical comparison of prednisolone and betamethasone in rheumatoid arthritis. *Eur J Clin Pharmacol* 1982; 23(4):321-5
35. McAllister WA, Thompson PJ, Al-Habet SM *et al.* Rifampicin reduces effectiveness and bioavailability of prednisolone. *Br Med J (Clin. Res)* 1983; 286(6369):923-5
36. Meffin PJ, Wing LM, Sallustio BC *et al.* Alterations in prednisolone disposition as a result of oral contraceptive use and dose. *Br J Clin Pharmacol* 1984; 17(6):655-64
37. Mendenhall CL, Anderson S, Garcia-Pont P *et al.* Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *N Engl J Med* 1984; 322(23):1464-70

38. Milov DE, Hill M, Andres JM *et al.* Measurement of plasma prednisolone level to evaluate a prednisone treatment failure in an adolescent with Crohn=s disease. *J Ped Gastroenterol & Nutrition* 1989; 8(3):404-7
39. Milsap RL, George DE, Szeffler SJ *et al.* Effect of inflammatory bowel disease on absorption and disposition of prednisolone. *Dig Dis Sci* 1983; 28(2):161-8
40. Morris PJ, Chan L, French ME *et al.* Low dose oral prednisolone in renal transplantation. *Lancet* 1982; 1(8271):525-7
41. Olivesi A. Modified elimination of prednisolone in epileptic patients on carbamazepine monotherapy, and in women using low-dose oral contraceptives. *Biomedicine & Pharmacotherapy* 1986; 40(8):301-8
42. Olivesi A. Normal absorption of oral prednisolone in children with active inflammatory bowel disease, including cases with proximal to distal small bowel involvement. *Gastroenterol Clin Biol* 1985; 9(8-9):564-71
43. Orta-Sibu N, Chantler C, Bewick M *et al.* Comparison of high-dose intravenous methylprednisolone with low-dose oral prednisolone in acute renal allograft rejection in children. *Br Med J (Clin. Res)* 1982; 285(6337):258-60
44. Pantin CF, Stead RJ, Hodson ME *et al.* Prednisolone in the treatment of airflow obstruction in adults with cystic fibrosis. *Thorax* 1986; 41(1):34-8
45. Papadakis J, Brown CB, Camaron JS *et al.* High versus low dose corticosteroids in recipients of cadaveric kidneys: prospective controlled trial. *Br Med J (Clin.Res)* 1983; 286(6371):1097-1100
46. Pickup ME. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1979; 4(2):111-28
47. Pimlott SJ, Addy M. Evaluation of a method to study the uptake of prednisolone sodium phosphate from different oral mucosal sites. *CLAO J* 1993; 19(3):166-8
48. Powell-Jackson PR, Gray BJ, Heaton RW *et al.* Adverse effect of rifampicin administration on steroid-dependent asthma. *Am Rev Respir Dis* 1983; 128(2):307-10
49. Reece PA, Disney AP, Stafford I *et al.* Prednisolone protein binding in renal transplant patients. *Br J Clin Pharmacol* 1985; 20(2):159-62
50. Renner E, Horber FF, Jost G *et al.* Effect of liver function on the metabolism of prednisone and prednisolone in humans. *Gastroenterol* 1986; 90(4): 819-28

51. Robertson AS, Gove RI, Wieland GA *et al.* A double-blind comparison of oral prednisolone 40 mg/day with inhaled beclomethasone dipropionate 1500 ug/day in patients with adult onset chronic obstructive airways disease. Department of thoracic Medicine, East Birmingham Hospital, England. *Eur J Respir Dis (Suppl)* (DENMARK) 1986; 146:565-9
52. Rudolf M. Trials of steroids in patients with chronic airflow obstruction. *Postgrad Med J* 1983; 59 Suppl3:68-70
53. Shaffer JA, Williams SE, Turnbeg LA *et al.* Absorption of prednisolone in patients with Crohn's disease. *Gut*, March 1983; 24(3):182-6
54. Sharma MP, Duphare HV, Dasarathy S. A prospective randomized double-blind trial comparing prednisolone and 4-aminosalicylic acid enemas in acute distal ulcerative colitis. *J Gastroenterol & Hepatol* 1992; 7(2):173-7
55. Shetty KR, Wang RIH. Using Corticosteroids effectively. *Drug Therapy* 1975; 121-26
56. Sirgo RA, Rocci ML Jr., Ferguson RK *et al.* Effects of cimetidine and ranitidine on the conversion of prednisone to prednisolone. *Clin Pharmacol Ther* 1985; 37(5):534-8
57. Sousa FJ. The bioavailability and therapeutic effectiveness of prednisolone acetate vs. prednisolone sodium phosphate: a 20-year review. *Review CLAO J* 1991; 17(4):282-4
58. Taha IA, Ahmad RA, Gray H *et al.* Plasma melphalan and prednisolone concentrations during oral therapy for multiple myeloma. *Cancer Chemother Pharmacol* 1982; 9(1):57-60
59. Tauber U, Haack D, Nieuweboer B *et al.* The pharmacokinetics of fluocortolone and prednisolone after intravenous and oral administration. *Int J Clin Pharmacol Ther Toxicol* 1984; 22(1)
60. Uekama K, Otagiri M, Uemura Y *et al.* Improvement of oral bioavailability of prednisolone by beta-cyclodextrin complexation in humans. *J Pharmacobiodyn* 1983; 6(2):124-7
61. Uribe M, Go VL. Corticosteroid pharmacokinetics in liver disease. *Clin Pharmacokinet* 1979; 4(3):233-40
62. Wald JA, Law RM, Ludwig EA *et al.* Evaluation of dose-related pharmacokinetics and pharmacodynamics of prednisolone in man. *J Pharmacokinetics & Biopharmaceutics* 1992; 20(6):567-89

63. Webb MS, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18 months. *Arch Dis Child* 1986; 61(1):15-9
64. Webb JR. Dose response of patients to oral corticosteroid treatment during exacerbations of asthma. *Br Med J Clin Res* 1986; 292(6527):1045-7
65. Yamashita SK, Ludwig EA, Middleton E Jr. *et al.* Lack of pharmacokinetic and pharmacodynamic interactions between ketoconazole and prednisolone. *Clin Pharmacol & Therapeutics* 1991; 49(5):558-70
66. Yokosuka O, Omata M, Imazeki F *et al.* Combination of short-term prednisolone and adenine arabinoside in the treatment of chronic hepatitis B. A controlled study. *Gastroenterology* 1985; 89(2):246-51