PRODUCT INFORMATION

REDIPRED®
(prednisolone sodium phosphate oral liquid)

NAME OF THE DRUG:
Prednisolone sodium phosphate.
Chemical name: 11ß,17,21-Trihydroxypregna-1.4-diene-3,20 dione-21-(disodium phosphate)
Chemical Abstracts No. [125-02-0]
Structural formula:

![Structural formula of Prednisolone sodium phosphate](image)

DESCRIPTION:
REDIPRED contains the active prednisolone sodium phosphate 6.72 mg/mL which is equivalent to 5 mg prednisolone. It also contains the inactive ingredients sorbitol solution (70%) non-crystallising, disodium edetate, sodium phosphate-monobasic, sodium phosphate-dibasic anhydrous, methyl hydroxybenzoate, propyl hydroxybenzoate, artificial raspberry flavour 500006U and water-purified.

PHARMACOLOGY:
Prednisolone is a synthetic glucocorticoid with the general properties of the corticosteroids. Prednisolone exceeds hydrocortisone in glucocorticoid and anti-inflammatory activity, being about three times more potent on a weight basis than the parent hormone, but is considerably less active than hydrocortisone in mineralocorticoid activity.

Prednisolone like hydrocortisone is a potent therapeutic agent influencing the biochemical behaviour of most tissues of the body.

The mechanism of action of corticosteroids is thought to be by control of protein synthesis. Corticosteroids react with receptor proteins in the cytoplasm of sensitive cells in many tissues to form a steroid-receptor complex.

Corticosteroids are palliative symptomatic treatment by virtue of their anti-inflammatory effects; they are never curative.
Pharmacokinetics
Prednisolone sodium phosphate is a pro-drug, hydrolysed in-vivo to prednisolone by alkaline phosphatase at the intestinal wall prior to absorption.

Prednisolone is rapidly and well absorbed ($t_{\text{max}} = 1-2$ hours) from the gastrointestinal tract following oral administration. Prednisolone is 90-95% protein-bound, less so at higher doses. The apparent volume of distribution for unbound prednisolone is $1.5 \pm 0.2$ L/kg.

It is eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolised mainly in the liver. Approximately 7-15% of an oral dose of prednisolone is excreted as unchanged prednisolone in the urine, the remainder being recovered as a variety of metabolites, including sulphate and glucuronide conjugates.

INDICATIONS:
Wherever corticosteroid therapy is indicated.

CONTRAINDICATIONS:
Uncontrolled infections; systemic fungal infections; known hypersensitivity to prednisone or prednisolone or any of the excipients in the liquid.

PRECAUTIONS:
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.

During prolonged corticosteroid therapy, adrenal suppression and atrophy may occur and secretion of corticotrophin may be suppressed. Duration of treatment and dosage appear to be important factors in determining suppression of the pituitary adrenal axis and response to stress on cessation of steroid treatment. The patient's liability to suppression is also variable. Some patients may recover normal function rapidly. In others, the production of hydrocortisone in response to the stress of infections, surgical operations or accident may be insufficient, and death results. Therefore, withdrawal of corticosteroids should always be gradual.

Abrupt withdrawal of corticosteroid therapy may precipitate acute adrenal insufficiency (see ADVERSE REACTIONS). In some cases, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been under treatment.

Because prednisolone manifests little sodium retaining activity, the usual early sign of hydrocortisone overdosage (ie. increase in bodyweight due to fluid retention) is not a reliable index of prednisolone overdosage. Hence recommended dose levels should not be exceeded, and all patients receiving prednisolone should be under close medical supervision. All precautions pertinent to the use of hydrocortisone apply to REDIPRED.
Use with caution in the following circumstances:
Use with caution in patients with impaired hepatic function, a reduction of dosage may be necessary. In treating chronic active liver disease with the drug, major adverse reactions such as vertebral collapse, diabetes, hypertension, cataracts and Cushing's syndrome occur in about 30% of patients.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection. Caution must also be used in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension and myasthenia gravis, when steroids are used as direct or adjunctive therapy.

Use with caution in patients with epilepsy, diabetes mellitus, uraemia and in the presence of diminished cardiac reserve or congestive heart failure. (see ADVERSE REACTIONS).

The possibility of development of osteoporosis should be an important consideration in initiating and managing corticosteroid therapy, especially in post menopausal women (see ADVERSE REACTIONS).

The risk of gastrointestinal ulceration or hemorrhage is increased when alcohol is used concurrently with glucocorticoids.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

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

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses. Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

Infection:
Corticosteroids may mask some signs of infection (such as fever and inflammation), and new infections may appear during their use. There may be decreased resistance and inability to localise infection when corticosteroids are used. Susceptibility to infection is not specific for any particular bacterial or fungal pathogen.

Patients should not be vaccinated with live vaccines while on corticosteroid therapy. Other immunisation procedures should not be undertaken in patients on corticosteroid therapy, especially on high doses, because of possible hazards of neurological complications and lack of antibody response. Immunization procedures may be undertaken in patients receiving corticosteroids as replacement therapy.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zooster immune globulin (VZIG) or pooled intravenous
immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Patients with active or doubtfully quiescent tuberculosis should not be given REDIPRED except as adjuncts to treatment with tuberculostatic drugs as reactivation of the disease may occur. Chemoprophylaxis is indicated during prolonged corticosteroid therapy.

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

Check the following before use:
During long courses of treatment, laboratory and metabolic studies should be made. Fluid retention should be watched for via a fluid balance chart and daily weighing. Sodium intake may need to be reduced to less than 1 g daily and potassium supplements may be necessary.

Use in Children:
Children on long term steroids must be carefully observed for potential serious adverse reactions such as obesity, growth retardation, osteoporosis and adrenal suppression.

Use in Elderly:
Caution is recommended for elderly patients as they are more susceptible to adverse reactions.

Carcinogenicity/Mutagenicity:
In male rats, administration of prednisolone in the drinking water at a daily dose level of 0.4 mg/kg for two years caused an increased incidence of hepatocellular tumours. Similar results were obtained with triamcinolone acetonide and budesonide, indicating a class effect of glucocorticosteroids. The hepatocarcinogenic response to these drugs does not appear to be related to genotoxic activity.

Use in Pregnancy: Category A of Australian Categorisation of Risk of Drug Use in Pregnancy.

In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformations) and abortion. These findings do not seem to be relevant to humans. Reduced placental and birth weight have been recorded in animals and humans after long term treatment. Since the possibility of suppression of the adrenal cortex in the new born baby after long term treatment must be considered, the needs of the mother must be carefully weighed against the risk to fetus when prescribing corticosteroids. The short term use of corticosteroids antepartum for the prevention of respiratory distress syndrome does not seem to pose a risk to the fetus or the newborn infant. Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

Use in Lactation:
The drug is excreted in breast milk; therefore, administration to nursing mothers is not recommended.

Interactions with other drugs:
The following drug interactions with corticosteroids have been selected on the basis of their potential clinical significance: antacids, antidiabetic agents (oral or insulin), digitalis glycosides, diuretics, drugs which induce hepatic microsomal enzymes, such as barbiturates,
phenytoin and rifampicin; potassium supplements, ritodrine, sodium-containing medications or foods, somatrem or somatropin, vaccines, live viruses or other immunisations.

Convulsions have been reported with concurrent use of methylprednisolone and cyclosporin. Since concurrent use of these agents results in a mutual inhibition of metabolism, it is possible that adverse effects associated with the individual use of either drug may be more apt to occur.

Drugs that induce hepatic enzymes such as phenobarbital, phenytoin and rifampicin may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response.

Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and thus decreased their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.

The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

**Effects on Laboratory Tests:**
Glucocorticoids may decrease $I_{131}$ uptake and protein-bound iodine concentrations, making it difficult to monitor the therapeutic response of patients receiving the drugs for thyroiditis. Glucocorticoids may produce false-negative results in the nitroblue tetrazolium test for systemic bacterial infection. Glucocorticoids may suppress reactions to skin tests.

**ADVERSE EFFECTS:**
Short-term administration of REDIPRED, even in massive dosages, is unlikely to produce harmful effects. The majority of adverse reactions from corticosteroids are those resulting from withdrawal or from prolonged use of high doses.

The side effects associated with the use of corticosteroids in the large doses necessary to produce a therapeutic response result from excessive action on electrolyte balance: excessive action on other aspects of metabolism including gluconeogenesis; the action on tissue repair and healing; and an inhibitory effect on the secretion of corticotrophin by the anterior pituitary gland. Disturbance of electrolyte and water balance is manifest in sodium retention with oedema and hypertension, and in the increased excretion of potassium with the development of hypokalaemic alkalosis. In extreme cases cardiac failure may be induced. Disturbances of electrolyte balance are common with the naturally occurring corticotrophins, cortisol, deoxycortone and hydrocortisone but are less frequent with the synthetic derivatives, prednisone and prednisolone. Other metabolic effects include mobilisation of calcium and phosphorus with osteoporosis and spontaneous fractures; nitrogen depletion and hyperglycaemia with accentuation or precipitation of the diabetic state. The insulin requirements of diabetic patients are increased and appetite is often increased.
The effect on tissue repair manifests as peptic ulceration with haemorrhage and perforation, delayed wound healing and increased liability to infection. Increased susceptibility to all kinds of infection, including sepsis, fungal and viral infection, has been reported.

Large doses of corticosteroids or corticotrophins may produce symptoms typical of hyperactivity of the adrenal cortex, with moonface, buffalo hump, flushing striae and acne sometimes leading to a fully developed Cushing’s syndrome. If administration of the hormone is discontinued immediately on the appearance of these symptoms, they are usually reversed but such sudden cessation may be dangerous. The dose of corticosteroid required to cause a decrease or absence of corticotrophin in the blood with consequent atrophy of the adrenal cortex and the time required for its occurrence are very variable. Acute adrenal insufficiency with loss of consciousness may occur during prolonged treatment or on cessation of treatment and may be precipitated by an infection or trauma.

Growth retardation in children has been reported and in this respect cortisone is only 1/10 as potent as prednisone and prednisolone. Other toxic effects include mental and neurological disturbances, intracranial hypertension and, on sudden reduction of dosage during the treatment of rheumatoid arthritis, fatalities attributed to lesions of small arteries and arterioles similar to polyarteritis.

Infections may be masked since corticosteroids have marked anti-inflammatory and antipyretic properties and may produce a feeling of well-being. The administration of corticosteroids may also cause a reduction in the number of circulating lymphocytes. Muscular weakness in an occasional side effect of most corticosteroids, particularly when they are taken in large doses.

Toxic effects occur with all corticosteroid preparations and their incidence rises steeply if dosage increases much above 8mg daily of prednisolone or its equivalent.

Postmarketing Reaction Frequencies

(>5%)

**Gastrointestinal:** Increased appetite; indigestion

**Neurological:** Nervousness or restlessness; insomnia

(1-5%)

**Dermatological:** Local allergic reaction

**Gastrointestinal:** Pancreatitis and ulcerative oesophagitis can occur. Peptic ulceration is an occasional complication. The high incidence of haemorrhage and perforation in these ulcers and the insidious nature of their development make them severe therapeutic problems. Some investigators believe the available evidence does not support the conclusion that steroids cause ulcers. Others feel that only patients with rheumatoid arthritis have an increased incidence of ulcers. It has been proposed that the glucocorticoids alter the mucosal defence mechanism.

**Ophthalmological:** Prolonged use of glucocorticoids may result in posterior subcapsular cataracts (particularly in children), exophthalmos, or increased intraocular pressure which may result in glaucoma or may occasionally damage the optic nerve and in rare cases, lead to blindness. Establishment of secondary fungal and viral infections of the eye may also be enhanced.
Biochemical: All glucocorticoids increase gluconeogenesis. Glucose tolerance and sensitivity to insulin are decreased but provided pancreatic islet function is normal carbohydrate metabolism will not be noticeably deranged. Steroid diabetes has been reported to develop in one fifth of patients treated with high glucocorticoid dosage. High dose corticosteroid therapy may induce marked hypertriglyceridaemia with milky plasma.

(<1%)

Dermatological: Dermatological adverse effects of corticosteroids include impaired wound healing, facial plethora, increased sweating, easy bruising, hirsutism, an acneiform eruption on the face, chest and back, red striae on the thighs, buttocks and shoulders. Several months of high dose therapy can often result in thinning of skin. Dermatologic manifestations of hypersensitivity to the corticosteroids include hives and/or allergic dermatitis, urticaria, and angioedema.

Corticosteroid induced purpura resembles senile purpura. This purpura usually occurs on extensor surfaces, dorsum of the hand, and radial aspect of the forearm.

Neurological: Adverse neurological effects have included headache, vertigo and increased motor activity, ischemic neuropathy, EEG abnormalities and seizures. Large doses can cause behavioural and personality changes ranging from nervousness, euphoria or mood swings to psychotic episodes which can include both manic and depressive states, paranoid states and acute toxic psychoses.

It is no longer believed that previous psychiatric problems predispose to behavioural disturbances during therapy with glucocorticoids. Conversely, the absence of a history of psychiatric illness is no guarantee against the occurrence of psychosis during hormonal therapy.

Endocrine: The endocrine effects of the glucocorticoids involve variously the hypothalamic pituitary adrenal axis; the parathyroid and thyroid. There are also metabolic effects, primarily involving the carbohydrates. Suppression of growth may occur in children.

Cushing's syndrome may result from prolonged elevation of plasma glucocorticoid levels.

Corticosteroids have also been reported to increase or decrease motility and number of sperm in some men. Disorders of menstruation are common.

Antagonism occurs between the parathyroids and hypercorticism. Latent hypoparathyroidism may be unmasked by administration of corticosteroids. The phosphate retention occurring in renal failure caused by adrenal insufficiency may also make hypoparathyroidism manifest.

Gastrointestinal: Adverse gastrointestinal effects of corticosteroids include nausea, vomiting, anorexia (which may result in weight loss), diarrhoea or constipation, abdominal distension and gastric irritation.

Cardiovascular: The mineralocorticoid activity of a steroid may lead to salt and water retention which can also result in hypertension. Hypokalaemia can lead to arrhythmias and cardiac arrest.
**Musculoskeletal:** Osteoporosis and vertebral compression fractures can occur in patients of all ages. Osteoporosis is an indication for withdrawal of therapy.

Myopathy, characterised by weakness of the proximal musculature of arms and legs and their associated shoulder and pelvic muscles, is occasionally reported in patients taking large doses of corticosteroids. It may occur soon after treatment is begun and be sufficiently severe to prevent ambulation. It is an indication for withdrawal of therapy.

Avascular aseptic necrosis of bone has often been described and preferentially involves the femoral and humeral head.

**Withdrawal Adverse Effects**
Muscle weakness, hypotension, hypoglycaemia, headache, nausea, vomiting, restlessness and muscle and joint pain. Muscle weakness and stiff joints may persist for three to six months after discontinuation of treatment. Adverse reactions from corticosteroids are those resulting from withdrawal or from prolonged use of high doses.

The following adverse reactions have also been reported, however, there is no information on their incidences.

**General:** Retardation of growth by long term corticosteroid treatment in children.

**Haematological:** Corticosteroids will increase the total WBC count, with an increase in neutrophils and a decrease in monocytes, lymphocytes and eosinophils.

**Immunological:** The frequency and severity of clinical infections increase during glucocorticoid therapy.

**Serious or Life Threatening Reactions:** Suppression of the hypothalamic pituitary adrenal axis is one of the consequences of repeated administration of glucocorticoids (see PRECAUTIONS). In some cases acute adrenal insufficiency after a period of glucocorticoid treatment has proved fatal.

**Neurological:** Latent epilepsy can be rendered manifest by corticosteroid treatment. Long term treatment may result in benign intracranial hypertension.

**DOSAGE & ADMINISTRATION:**

The severity, prognosis, expected duration of the disease, and the patient's reaction to medication are primary factors in determining dosage.

**Adults:**
The initial adult dosage may range from 20 to 40 mg daily, but can be 60 to 80 mg daily if necessary, depending on the disease being treated.

Maintenance dosage: Usually 5 to 20 mg daily.

In long term therapy the ideal dosage should not be greater than 40 mg per day so as to minimise side-effects. It is usually administered in 2-4 divided doses or as a single daily dose after breakfast or on alternate days.
Alternate-Day Therapy
Alternate-day therapy is the dosage regimen of choice for long-term oral glucocorticoid treatment of most conditions. In alternate-day therapy, a single dose is administered every other morning. This regimen provides relief of symptoms while minimizing adrenal suppression, protein catabolism, and other adverse effects. However, some patients may require daily glucocorticoid therapy because symptoms of the underlying disease cannot be controlled by alternate-day therapy.

Elderly:
As for adults - though the dose should be the minimum necessary to achieve the desired therapeutic effect.

Children:
Initial dosage: 0.5 mg/kg daily in three or four divided doses after food as in adults. This dosage can be doubled or trebled if necessary. Maintenance dosage: 0.125 to 0.25 mg/kg daily.

For infants and children, the recommended dosage should be governed by the same considerations as adults rather than by strict adherence to the ratio indicated by age or body weight.

The following therapeutic guidelines should be kept in mind for all therapy with corticosteroids:

Dosage should be decreased or discontinued gradually when the drug has been administered for more than a few days to avoid the risk of relative adrenal insufficiency (see PRECAUTIONS).

Continued supervision of the patient after cessation of corticosteroids is essential, since there may be a reappearance of severe manifestations of the disease for which the patient was treated.

In general, initial dosage should be maintained or adjusted until the anticipated response is observed. The dose should then be gradually reduced until the lowest dose which will maintain an adequate clinical response is reached.

Stress and Intercurrent Illness: In patients on long term corticosteroid therapy subjected to stress from trauma or infection, steroid dosage should generally be increased to cover the stressful period. For mild infections without fever, no increase is necessary. For more serious infections, the dose of prednisone/prednisolone should be doubled (to a maximum of 20 mg daily, if the usual dosage was below this).

Adrenocortical Insufficiency: Drug induced secondary adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimised by gradual reduction of dosage (see PRECAUTIONS). 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. If the patient is receiving steroids already, dosage may have to be increased.
OVERDOSAGE:

Treatment is symptomatic with the dosage being reduced or the drug withdrawn.

Contact the Poisons Information Centre on 131126 for management of overdose.

PRESENTATION:

REDIPRED prednisolone (as sodium phosphate) 5 mg/1 mL oral liquid is a raspberry flavoured, clear, colourless to slightly yellow solution.

Packs of 30 mL and 100 mL* bottles.

(* not currently marketed in Australia)

STORAGE:

Store below 30°C. Protect from light.

Discard 4 weeks after opening.

POISONS SCHEDULE:

S4.

NAME AND ADDRESS OF SPONSOR:

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos St
St Leonards NSW 2065
Australia

DATE OF TGA APPROVAL:

Approved by the Therapeutic Goods Administration: 19 February 1998
Date of most recent amendment: 12 October 2011