AUSTRALIAN PRODUCT INFORMATION

PREDMIX (prednisolone sodium phosphate) oral liquid

1 NAME OF THE MEDICINE

Prednisolone sodium phosphate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Predmix contains the active ingredient prednisolone sodium phosphate 7.06 mg/1 mL equivalent to prednisolone 5 mg/1 mL.

It contains excipients with known effect, methyl hydroxybenzoate and propyl hydroxybenzoate. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Predmix is a clear, colourless liquid free from haze and substantially free from particulate matter.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Whenever corticosteroid therapy is indicated.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage should be individualised according to severity of condition and response of patient.

Children:
Asthma: 1 mg/kg once daily

Croup: 1 mg/kg/dose every 8-12 hours for 48 hours

Physiological replacement: 4-5 mg/m^2/day (Preferable to use shorter acting steroid to avoid growth suppression)

Infantile spasms, intractable epilepsy: 2 mg/kg/day

Nephrotic syndrome: 2 mg/kg/day (max 80 mg/day) until protein free urine for 5 days. Increase to 4 mg/kg/day (max 120 mg/day) if no response within 28 days.

Autoimmune liver disease, Crohn's disease, Ulcerative colitis: 2 mg/kg/day for initial control, reducing over 2 months to a maintenance dose of 5 mg/day or less (or cease).

Adults:
10-40 mg daily (up to 100 mg can be used in divided doses) reducing gradually when control is achieved to the lowest possible dose (5-20 mg).

4.3 CONTRAINDICATIONS

Patients with active or doubtfully quiescent tuberculosis should not be given Predmix Oral Liquid except as an adjunct to treatment with tuberculostatic drugs.

Systemic fungal infections and known hypersensitivity to prednisolone or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Scleroderma renal crisis:
Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Corticosteroids should be used with caution in the presence of diminished cardiac reserve or congestive heart failure, in patients with diabetes mellitus, epilepsy, infectious diseases, chronic renal failure, uraemia, peptic ulcer, osteoporosis, psychoses or severe psychoneuroses and in elderly persons.

Corticosteroids may mask some signs of infection (such as fever and inflammation), and new infections may appear during their use. Infections with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic infections, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressant agents that affect cellular immunity, humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

There may be decreased resistance to infection and inability to localise infection when corticosteroids are used. Children who are on immunosuppressant drugs are more susceptible to infection than healthy children. Chickenpox and measles, for example, can have a more serious course in these children. Particular care should be taken to avoid exposure in these children (and immunosuppressed adults).

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

Withdrawal symptoms:
During prolonged treatment with corticosteroids, adrenal suppression and atrophy may occur and secretion of corticotrophin may be suppressed. Sudden withdrawal of Predmix Oral Liquid may then precipitate acute adrenal insufficiency with 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 treatment has been discontinued. In some instances withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been under treatment.

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. Individual liability to suppression is also important. Some patients may recover normal function rapidly on discontinuing steroid therapy. In others, the production of hydrocortisone in response to the stress of infections, surgical operations or accident, may be insufficient, and death results. Withdrawal of corticosteroids should therefore always be gradual unless sudden withdrawal is absolutely necessary.

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

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.

Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and 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.

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.

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.

Steroids should be used with caution in nonspecific 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 and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Use in the elderly
Corticosteroids should be used with caution in elderly persons.

Paediatric use
Children on long term therapy should be monitored carefully for signs of serious adverse reactions including growth retardation, adrenal suppression, osteoporosis and obesity.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 that 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.

Drugs that induce hepatic microsomal enzymes, such as barbiturates, 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 decrease their clearance. Therefore, the dose of corticosteroid should be titrated to avoid steroid toxicity. Corticosteroids may increase the clearance of chronic high dose aspirin. This could lead to decreased salicylate serum levels or increase the risk of salicylate toxicity when corticosteroid is withdrawn. Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypothrombinemia.

The effects 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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No data available.

Use in pregnancy – Pregnancy Category A
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 the fetus when prescribing these drugs. 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Short-term administration of Predmix Oral Liquid, even in doses at the high end of the dose range is unlikely to produce harmful effects associated with chronic usage but short term administration may be associated with adverse effects related to the pharmacology of the drug.

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 balance is manifest in the retention of sodium and water, 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 corticotrophin, cortisone, deoxycortone and hydrocortisone but are less frequent with the synthetic derivatives, prednisone and prednisolone. Other metabolic effects lead to 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 is manifest in peptic ulceration with haemorrhage and perforation, delayed wound healing and increased liability to infection. Increased susceptibility to all kinds of infection, including sepsis, fungus infections and viral infections have been reported.

Large doses of corticosteroids or of corticotrophins may produce symptoms typical of hyperactivity of the adrenal cortex, with moon face, 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 have been attributed to lesions of small arteries and arterioles similar to polyarteritis.

Infections may be masked since corticosteroids have marked anti-inflammatory and anti-pyretic 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 is 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, however, 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 that the available evidence does not support the conclusion that steroids cause ulcers. Others feel that only patients with rheumatoid arthritis have an increased risk of ulcers. It has been proposed that 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 acneform 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 the skin. Dermatological manifestations of hypersensitivity to corticosteroids include hives and/or allergic dermatitis, urticaria and angioedema. Corticosteroid induced purpura resembles senile purpura and usually occurs on extensor surfaces, the dorsum of the hand and the radial aspect of the forearm.

Neurological: Adverse neurological effects have included headache, vertigo and increased motor activity, ischaemic 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 the 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 the motility and number of sperm in some men. Disorders of menstruation are common.

Antagonsim 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 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 shortly after initiation of therapy 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 3 to 6 months after discontinuation of therapy. 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 incidence.

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.

Severe or life-threatening reactions: Suppression of the hypothalamic-pituitary-adrenal axis is one of the consequences of repeated administration of glucocorticoids (see section 4.4, Special Warnings and Precautions for Use). 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.

Eye disorders: blurred vision.

Scleroderma renal crisis: frequency 'unknown'. Amongst the different subpopulations the occurrence of scleroderma renal crisis varies. The highest risk has been reported in patients with diffuse systemic sclerosis. The lowest risk has been reported in patients with limited systemic sclerosis (2%) and juvenile onset systemic sclerosis (1%).

Cardiac disorders: frequency 'unknown'. Bradycardia has been reported following high doses.

4.9 OVERDOSE

There is no specific antidote. Toxic effects are signs of overdosage and should be treated symptomatically and dosage reduced or the drug withdrawn. During long courses of treatment, laboratory and metabolic studies should be made. Fluid retention should be watched for via fluid balance chart and daily weighing. Sodium intake may need to be reduced and potassium supplements may be necessary.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Prednisolone sodium phosphate is readily hydrolysed in vivo to prednisolone and the pharmacology and clinical actions are therefore those of prednisolone.

Prednisolone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties which include; promotion of gluconeogenesis, increased deposition of glycogen in the liver, inhibition of the utilisation of glucose, anti-insulin activity, increased catabolism of protein, increased lipolysis, stimulation of fat synthesis and storage, increased glomerular filtration rate and resulting increase in

urinary excretion of urate (creatinine excretion remains unchanged) and increased calcium excretion. Some of the properties of prednisolone reproduce the physiological actions of endogenous glucocorticoids whereas others not reflecting any of the adrenal hormones' normal functions are seen with administration of larger doses of the drug.

Depressed production of eosinophils and lymphocytes occurs but erythropoiesis and production of polymorphonuclear leucocytes are stimulated. Anti-inflammatory processes (oedema, fibrin deposition, capillary dilatation, migration of leucocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrisation) are inhibited.

Prednisolone can stimulate secretion of various components of gastric juice. Stimulation of the production of corticotrophin may lead to suppression of endogenous corticosteroids. Prednisolone has slight mineralocorticoid activity whereby entry of sodium into cells and loss of intracellular potassium is stimulated. This is particularly evident in the kidney where rapid ion exchange leads to sodium retention and hypertension.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Prednisolone is absorbed rapidly from the gastrointestinal tract. Maximum plasma concentrations (C_{max}) of approximately 140 nanogram/mL are achieved at 1.6 hours (t_{max}) following administration of a 10 mg dose (2 mL Predmix Oral Liquid). The elimination half life ($t_{1/2}$) of prednisolone is approximately 2 hours. Predmix Oral Liquid has been shown to be bioequivalent to prednisolone oral tablets (Panafcortelone).

Distribution
Prednisolone is 90 to 95% bound to plasma proteins

Metabolism
Prednisolone is conjugated in the liver and to some extent in the kidney

Excretion
Prednisolone is excreted in the urine as free and conjugated metabolites, with 7-15% of an administered dose excreted as unchanged prednisolone.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
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 glucocorticoids. The hepatocarcinogenic response to these drugs does not appear to be related to genotoxic activity.

Carcinogenicity
The carcinogenic potential of prednisone has been evaluated in mice at oral doses up to 5 mg/kg/day for 18 months. No carcinogenic effect was noted in the mouse.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Propylene glycol, methyl hydroxybenzoate, propyl hydroxybenzoate, dibasic sodium phosphate dodecahydrate, monobasic sodium phosphate, disodium edetate and water-purified.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2º-8ºC. Refrigerate. Do not freeze.

Discard 4 weeks after opening.

6.5 NATURE AND CONTENTS OF CONTAINER

Bottles of 30 mL.

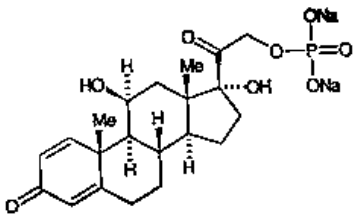
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

It is a white or slightly yellow hygroscopic powder, soluble 1 in 3 or 4 of water and slightly soluble in alcohol. A 0.5% liquid has a pH of 7.5 to 9.0. Chemical name: 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione disodium 21-phosphate. Formula: C_{21} H_{27} Na_2 O_8 P, Molecular weight: 484.4

Chemical structure



CAS number
125-02-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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

Australia

9 DATE OF FIRST APPROVAL

19/01/1999

10 DATE OF REVISION

20 April 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Updated to the revised Australian product information format.
4.4 & 4.8	Addition of scleroderma renal crisis (SRC) safety signal
4.8	Addition of 'bradycardia' AE as an unknown frequency following high doses