NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Redipred oral solution 5 mg/mL.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Redipred contains 6.72 mg/mL of the active ingredient, prednisolone sodium phosphate (equivalent to prednisolone 5 mg/mL).

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Redipred is a preserved, raspberry flavoured, clear, colourless to slightly yellow aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Redipred is used wherever corticosteroid therapy is indicated.

4.2 Dose and method of administration

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

Children
Acute asthma requiring oral steroids:
2 mg/kg at once, up to a maximum of 40 mg. Thereafter dose at 2 mg/kg once daily up to a maximum of 40 mg per day, and for up to a total of five days. Redipred should be taken in the morning after food. No gradual decrease of the dose is required.

Other indications:
Initial dosage: 0.5 mg/kg/day in three or four divided doses after food. This dosage can be doubled or trebled if necessary.

Maintenance dosage: 0.125 to 0.25 mg/kg/day.

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

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.

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

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 minimising 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.

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. 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.

4.3 Contraindications

Uncontrolled infections. Known hypersensitivity to prednisolone or prednisone, or any of the excipients in the oral liquid. Live virus immunisation.

4.4 Special warnings and precautions for use

Adrenocorticol insufficiency:
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 and depends on the dose, frequency, time of administration and duration of therapy. 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.

Symptoms of adrenal insufficiency include: malaise, muscle weakness, mental changes, muscle and joint pain, desquamation of the skin, dyspnoea, anorexia, nausea and vomiting, fever, hypoglycaemia, hypotension and dehydration.

Abrupt withdrawal of corticosteroids therapy may precipitate acute adrenal insufficiency. In some cases, withdrawal symptoms may simulate a clinical relapse of the disease for which the patient has been under treatment. Therefore, withdrawal of corticosteroids should always be gradual. A degree of adrenal insufficiency may persist for 6 to 12 months; therefore in any situation of stress occurring during that period steroid therapy may need to be reinstituted. Since mineralocorticoid secretion may be impaired, treatment with salt and/or mineralcorticosteroid may also be needed.

Because prednisolone manifests little sodium retaining activity, the usual early sign of hydrocortisone overdosage (i.e. 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.

General precautions:
Use with caution in patients with impaired hepatic function, a reduction of dosage may be necessary. In treating chronic 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 or in those with a family history of diabetes, uraemia and in the presence of diminished cardiac reserve or congestive heart failure.

The possibility of the development of osteoporosis should be an important consideration in initiating and managing corticosteroid therapy, especially in post-menopausal women.

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

Patients with active or doubtfully quiescent tuberculosis should not be given prednisolone except as adjuncts to treatment with tuberculostatic drugs as

reactivation of the disease may occur. Chemoprophylaxis is indicated during prolonged corticosteroid therapy.

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 and calcium supplements may be necessary.

Anti-inflammatory/immunosuppressive effects and infection:
Corticosteroids may mask some signs of latent 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.

Live vaccines are contraindicated in patients on high doses of corticosteroids and should be postponed until at least 3 months after stopping 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. Immunisation 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. Chicken pox 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, they should seek urgent medical attention. Therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chicken pox develops, treatment with antiviral agents may be considered.

Ocular effects:
Prolonged use of corticosteroids may produce subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. 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 which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Corticosteroids should only be initiated in patients with ocular herpes simplex with appropriate viral cover by ophthalmologists because of the risk of corneal scaring loss of vision and corneal perforation.

Psychiatric effects:
Patients and/or carers should be warned that potentially severe psychiatric reactions may occur. Symptoms typically emerge within a few days or weeks of starting treatment. Most patients recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients and/or carers should be encouraged

to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected.

Particular care is required when considering the use of corticosteroids in patients with existing or previous history of severe affective disorders.

Psychic derangements range from euphoria, insomnia, mood swings, personality changes and severe depression to frank psychotic manifestations.

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

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.

Children are at special risk from raised intracranial pressure.

Use in the elderly:
Caution is recommended for elderly patients as they are more susceptible to adverse reactions, especially osteoporosis, diabetes, hypertension, hypokalaemia, susceptibility to infection and thinning of the skin.

Carcinogenicity/mutagenicity:
In male rats, administration of prednisolone in the drinking water at a daily dose of 0.4mg/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.

Other conditions:
Caution is necessary when oral corticosteroids are used in patients with the following other conditions and frequent monitoring is necessary:

- Hypothyroidism
- Glaucoma
- Patients with a history of severe affective disorders particularly of steroid induced psychoses
- Previous steroid myopathy
- Patients with thromboembolic disorders
- Patients with Duchenne's muscular dystrophy since transient rhabdomyolysis and myoblobinuria have been reported following strenuous physical activity.

4.5 Interactions with other medicines and other forms of interaction

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, sodium-containing medications of foods, somatropin, vaccines, live viruses or other immunisations.

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.

Other interactions for oral and systemic corticosteroids:

Hepatic microsomal enzyme inhibitors:	Medicines that inhibit enzyme cytochrome P-450 isozyme 3A4 such as ketoconazole, cyclosporin or ritonavir may decrease glucocorticoid clearance. A reduction in corticosteroid dose may be needed to reduce the risk of adverse effects.
Non-steroidal anti-inflammatory drugs (NSAIDs):	Concomitant administration may increase the risk of GI ulceration. Aspirin should be used cautiously in conjunction with corticosteroids in patients with hypothrombinaemia. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Patients should be observed closely for adverse effects of either medicine.
Anticoagulants:	Response to anticoagulants may be reduced or less often enhance by corticosteroids. Close monitoring of the INR or prothrombin time is recommended.
Antifungals:	The risk of hypokalaemia may be increased with amphotericin.
Mifepristone:	The effects of corticosteroids may be reduced for 3-4 days after mifepristone.
Oestrogens:	Oestrogens may potentiate the effects of glucocorticoids. The dose of corticosteroid may need to be adjusted if oestrogen therapy is commenced or stopped.
Sympathomimetics:	There is an increased risk of hypokalaemia if high doses of corticosteroids are given with high doses of salbutamol, salmeterol, terbutaline or formoteral.

4.6 Fertility, pregnancy and lactation

Pregnancy: **Category A**
In animal experiments, corticosteroids have been found to cause malformations of various kinds (cleft palate, skeletal malformation) 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 newborn baby after long term treatment must be considered, the needs of the mother must be carefully weighted against the risk to the foetus 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 foetus or the newborn infant. Maternal pulmonary oedema has been reported with tocolysis and fluid overload.

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

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/.

Short term administration of Redipred, even in massive dosages, is unlikely to produce harmful effects. The majority of adverse reactions from corticosteroids are those from withdrawal or from prolonged use of high doses.

More common reactions

Gastrointestinal:
Adverse gastrointestinal effects of corticosteroids include nausea, vomiting, anorexia (which may result in weight loss), increased appetite (which may result in weight gain), 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.

Neurological:
Adverse neurological effects have included headache, vertigo, insomnia, dizziness, restlessness 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.

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.

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 with increased requirement for antidiabetic therapy, manifestation of latent diabetes mellitus, increased appetite and weight gain. Retardation of growth by long term corticosteroid treatment 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 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.

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.

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.

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.

Serious or life-threatening reactions:
Suppression of the hypothalamic pituitary adrenal axis is one of the consequences of repeated administration of glucocorticoids. In some cases acute adrenal insufficiency after a period of glucocorticoid treatment has proved fatal.

Less common reactions

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.

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

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 or rare diseases such as central serous chorioretinopathy (CSCR). Establishment of secondary fungal and viral infections of the eye may also be enhanced.

Withdrawal symptoms:
Muscle weakness, hypoglycaemia, headache, nausea, vomiting, anorexia leading to weight loss, lethargy, fever, restlessness and muscle and joint pain. Muscle weakness and stiff joints may persist for three to six months after discontinuation of treatment. Too rapid a reduction of corticosteroids following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death.

Other adverse effects for oral and systemic corticosteroids:

Gastro-intestinal:	Dyspepsia
Body as a whole:	Leucocytosis, hypersensitivity including anaphylaxis, thromboembolism, fatigue, malaise
Cardiovascular:	congestive heart failure in susceptible patients
Musculoskeletal:	tendon rupture, myalgia
Metabolic/nutritional:	potassium loss, negative nitrogen and calcium balance
Skin:	telangiectasia, acne, pruritis, rash
Nervous system:	Aggravation of schizophrenia and epilepsy suicidal ideation, mania, delusions, hallucinations, irritability anxiety, cognitive dysfunction. In adults the frequency of severe psychiatric reactions has been estimated to be 5-6%.
Eye disorders:	corneal or sclera thinning, papilloedema.
Anti-inflammatory and immunosuppressive effects:	Opportunistic infections, recurrence of dormant tuberculosis.

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Actions:
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 of virtue of their anti-inflammatory effects; they are never curative.

5.2 Pharmacokinetic properties

Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration. REDIPRED Oral Solution produces a 20% higher peak plasma level of prednisolone which occurs approximately 15 minutes earlier than the peak seen with tablet formulations. Prednisolone is 90-95% protein-bound, less so at higher doses. The apparent volume of distribution for unbound prednisolone is 1.5 ± 0.2 L/kg. Prednisolone is eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolised mainly in the liver and excreted in the urine as sulphate and glucuronide conjugates.

5.3 Preclinical safety data

Not relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol solution (70 per cent)(non-crystallising), disodium edetate, dibasic sodium phosphate, monobasic sodium phosphate, methyl hydroxybenzoate, propyl hydroxybenzoate, nature identical raspberry flavour 08-3326 (PI 892) and purified water.

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

18 months.

Once opened, Redipred is stable for 4 weeks. Product should not be used beyond the expiry date printed on the bottle.

6.4 Special precautions for storage

Store at or below 30ºC.

6.5 Nature and contents of container

30 mL & 100 mL PET bottles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pharmacy Retailing (NZ) Limited trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland, New Zealand

Telephone: (09) 918 5100
Email: aspen@aspenpharma.co.nz

9. DATE OF REVISION OF THE TEXT

19 October 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of Pheochromocytoma crisis safety signal.