Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Predsol Retention Enema 20 mg/100 ml Rectal Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 ml contains 20 mg prednisolone (as sodium phosphate salt).

Also contains Nipastat GL 75 (Butyl, Ethyl (E214), Methyl (E218), Propyl (E216) Hydroxybenzoates)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Rectal solution (Enema)
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Predsol Retention Enema provides local corticosteroid treatment for rectal and rectosigmoidal disease in ulcerative colitis and Crohn's disease.

4.2 Posology and method of administration

Adults
1 enema used nightly, for 2 to 4 weeks. Treatment may be continued in patients showing progressive improvement, but it should not be continued if the response has been inadequate. Some patients may relapse after an interval but are likely to respond equally well to a repeated course of treatment.

The enema is used each night on retiring. It may be warmed before administration by placing the bottle in a vessel of hot water for a few minutes. Before use, lie in bed on the left side with knees drawn up. Hold the bottle upwards. Place hand in the protective plastic cover and remove the cap from the bottle. Attach the nozzle and lubricate with petroleum jelly. Gently insert about half the length of the nozzle into the rectum. The bottle should then be squeezed gently until it is emptied, taking a minute or two to do so. The nozzle should then be removed from the rectum. Invert the plastic protective cover around the bottle and discard the whole unit. The patient should then roll over to lie face down for 3 to 5 minutes but may sleep in any comfortable position.

Although predsol enema is applied locally, it should be borne in mind that there is likely to be substantial systemic absorption, especially when the bowel is inflamed.

The volume of the enema is considered to be the optimum to ensure maximum coverage of the affected area. However, undesirable effects may be minimised by using for the minimum period. Frequent patient review is required to monitor therapeutic effect against disease activity.

Children

Predsol Retention Enema as packed is not suitable for use in children.

4.3 Contraindications

Use during remission of the disease.

Systemic or local infection unless specific anti-infective therapy is employed.
Hypersensitivity to any ingredient.

4.4 Special warnings and precautions for use

Use with extreme caution in patients with severe ulcerative colitis or Crohn's disease.

Suppression of the inflammatory response and immune function increases the susceptibility to infections and their severity. The clinical presentation may often be atypical and serious infections such as septicaemia and tuberculosis may be masked and may reach an advanced stage before being recognised.

Chickenpox is of particular concern since this normally minor illness may be fatal in immunosuppressed patients. Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunisation with varicella zoster immunoglobulin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Patients should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin may be needed.

Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

Corticosteroid treatment may reduce the response of the pituitary adrenal axis to stress, and relative insufficiency can persist for years after withdrawal of prolonged therapy. Withdrawal of corticosteroids after prolonged therapy must therefore always be gradual to avoid acute adrenal insufficiency, being tapered off over weeks or months depending on the duration of treatment.

During prolonged therapy any intercurrent illness, trauma or surgical procedure may require a temporary increase in dosage. If corticosteroids have been stopped following prolonged therapy they may need to be temporarily re-introduced.

Use with caution in patients with myasthenia gravis, non-specific ulcerative colitis, diverticulitis and fresh intestinal anastamoses.

<u>Special precautions</u>
Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary.

A. Osteoporosis (post-menopausal females are particularly at risk).

B. Hypertension or congestive heart failure.

C. Existing or previous history of severe affective disorders (especially previous steroid psychosis).

D. Diabetes mellitus (or a family history of diabetes).

E. History of tuberculosis.

F. Glaucoma (or a family history of glaucoma).

G. Previous corticosteroid-induced myopathy.

H. Liver failure - blood levels of corticosteroid may be increased, (as with other drugs which are metabolised in the

liver).

I. Renal insufficiency.

J. Epilepsy.

K. Peptic ulceration.

L. Hypothroidism

M. Recent myocardial infarction.

Patients should carry 'steroid treatment' cards which give clear guidance on the precautions to be taken to minimise risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Patients/and or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure (see also section 4.5 pharmacokinetic interactions that can increase the risk of side effects), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatments may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should also be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required with considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Use in the elderly
The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Systemic absorption of prednisolone should be borne in mind, especially when there is local inflammation. Thus the following interactions are possible:

Analgesics:
Increased risk of gastro-intestinal bleeding and ulceration with aspirin and non-steroidal anti-inflammatory drugs (NSAIDs); the renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

Antibacterials:
Rifamycins accelerate metabolism of corticosteroids (reduced effect); erythromycin inhibits metabolism of methylprednisolone and possibly other corticosteroids.
Fluoroquinolones: - Increased risk of tendon rupture.

Anticoagulants:
The efficacy of coumarins anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.

Antidiabetics:
Antagonism of hypoglycaemic effect.

Antiepileptics:
Carbamazepine, phenobartital, phenytoin and primidone accelerate metabolism of corticosteroids (reduced effect).

Antifungals:
Increased risk of hypokalaemia with amphotericin (avoid concomitant use unless corticosteroids are required to control reactions); ketoconazole inhibits metabolism of methylprednisolone and possibly other corticosteroids.

Antihypertensives:
Antagonism of hypotensive effect.

Antimuscarinics:
Decreased effect of antimuscarinics in myasthenia gravis.

Antivirals:
Ritonavir possibly increases plasma concentrations of prednisolone.

Cardiac Glycosides:
Increased toxicity if hypokalaemia occurs with corticosteroids.

Ciclosporin:
Increased plasma concentrations of prednisolone.

Cytotoxics:
Increased risk of haematological toxicity with methotrexate.

Diuretics:
Antagonism of diuretic effect; acetazolamide, loop diuretics, and thiazides increased risked of hypokalaemia.

Hormone antagonists:
Aminoglutethimide accelerates metabolism of corticosteroids (reduced effect).

Isoniazid :
Decreased isoniazid concentrations.

Licorice:
Increased corticosteroid levels.

Mifepristone:
Effects of corticosteroid may be reduced for 3-4 days after mifepristone.

Oestrogens and Progestogens:
Alteration in the plasma protein binding and metabolism of prednisolone caused by oestrogens, with or without progesterone, can result in exposure of women to increased levels of unbound prednisolone for prolonged periods of time.

Quetiapine:
Decreased quetiapine concentrations.

Somatropin:
The growth promoting effect of somatropin may be inhibited.

Sympathomimetics:
Increased risk of hypokalaemia if high does of corticosteroids given with high does of bambuterol, fenoterol, formoterol, ritodrine, salbutamol, salmeterol, and terbutaline.

Theophylline:
Increased risk of hypokalaemia.

Ulcer-healing drugs:
Carbenoxolone increases the risk of hypokalaemia.

Vaccines:
Live vaccines should not be given to individuals with impaired immune response as a result of treatment with large doses of corticosteroids.

4.6 Fertility, pregnancy and lactation

Topical administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate and intrauterine growth retardation. There may therefore be a very small risk of such effects in the human foetus. Also, hypoadrenalism may occur in the neonate. When corticosteroids are essential however, patients with normal pregnancies may be treated as though they were in the non-gravid state. Patients with pre-eclampsia or fluid retention require close monitoring.

Corticosteroids are excreted in small amounts in breast milk and infants of mothers taking pharmacological doses of steroids should be monitored carefully for signs of adrenal suppression.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The incidence of predictable undesirable effects, including hypothalamic-pituitary-adrenal (HPA) axis suppression correlates with the relative systemic potency of the drug, dosage, timing of administration and the duration of treatment. (see Warnings and Precautions).

Endocrine/Metabolic
Suppression of the hypothalamic-pituitary-adrenal axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea. Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy. Negative protein and calcium balance. Increased appetite.

Anti-inflammatory and immunosuppressive effects
Increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see Other Special Warnings and Precautions).

Blood and lymphatic system disorders:
Alteration in lipid levels (increases in total cholesterol, low density lipoproteins and triglycerides), porphyria, leukemoid reactions.

Musculoskeletal
Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, proximal myopathy.

Neuromuscular blockers
Antagonism of the neuromuscular blockade.

Fluid and electrolyte disturbance
Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis.

Neuropsychiatric

A wide range of psychiatric reactions including affective disorder (such as irritable, euphoric, depressed and labile mood and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common any may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to the 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown.

Psychological dependence. Increased intra-cranial pressure with papilloedema in children (pseudotumour cerebri), usually after treatment withdrawal. Aggravation of epilepsy.

Ophthalmic
Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases.Chorioretinopathy.

Cardiac
Myocardial rupture following recent myocardial infarction.

Gastrointestinal
Nausea, hiccups, dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis, candidiasis.

Dermatological
Impaired healing, skin atrophy, bruising, telangiectasia, striae, acne, dermatitis, increased sweating and toxic epidermal necrolysis.

General
Hypersensitivity including anaphylaxis has been reported. Leucocytosis. Thrombo-embolism.

Withdrawal symptoms and signs
Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and in severe cases this could be fatal. (see Other Special Warnings and Precautions).

A ‘withdrawal syndrome’ may also occur including; fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight.

Uncommon side effects include decreased or blurred vision, passing water more often than usual and increased thirst. Bleeding, blistering, burning, itching or pain in the rectum not present before treatment may also occur. Rare side effects include hallucinations and skin rashes or hives.

4.9 Overdose

Treatment is unlikely to be needed in cases of acute overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not applicable.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nipastat GL 75 (Butyl, Ethyl (E214), Methyl (E218), Propyl (E216) hydroxybenozoates)
Disodium edetate
Sodium dihydrogen phosphate dihydrate
Anhydrous disodium hydrogen phosphate
Sodium hydroxide (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container in the outer carton.

6.5 Nature and contents of container

Each 100ml single dose is supplied in a low density polyethylene bottle with a low density polyethylene cap and a separate PVC nozzle.

Seven bottles, plastic protective covers and instructions for use are supplied in each box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

RPH Pharmaceuticals AB
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8 MARKETING AUTHORISATION NUMBER

PA 1638/8/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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