

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Betnesol 500 microgram Soluble Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms (0.5 mg) betamethasone as betamethasone sodium phosphate.

Excipients: contains 20.9mg sodium per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soluble Tablet

Small, soluble, pink tablet engraved Betnesol Evans on one side and scored on the reverse.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

A wide variety of diseases may sometimes require corticosteroid therapy. Some of the principal indications are as follows.

Bronchial asthma, severe hypersensitivity reactions, anaphylaxis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, mixed connective tissue disease (excluding systemic sclerosis), polyarteritis nodosa; inflammatory skin disorders, including pemphigus vulgaris, bullous pemphigoid and pyoderma gangrenosum; minimal change nephrotic syndrome, acute interstitial nephritis; ulcerative colitis, Crohn's disease; sarcoidosis; rheumatic carditis; haemolytic anaemia (auto-immune), acute lymphoblastic and chronic lymphocytic leukaemias, malignant lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura; immunosuppression in transplantation.

4.2 Posology and method of administration

Betnesol Tablets are best taken dissolved in water, but they can be swallowed whole without difficulty. The lowest dosage that will produce an acceptable result should be used; when it is possible to reduce the dosage, this must be accomplished by stages. During prolonged therapy, dosage may need to be increased temporarily during periods of stress or in exacerbations of illness (see "Special Warnings and Special Precautions for Use").

Adults

The dose used will depend upon the disease, its severity, and the clinical response obtained. The following regimens are for guidance only.

Short-Term treatment

2 to 3mg daily for the first few days, subsequently reducing the daily dose by 250 or 500 micrograms (0.25 or 0.5mg) every two to five days, depending upon the response.

Rheumatoid arthritis

500 micrograms (0.5mg) to 2mg daily. For maintenance therapy the lowest effective dosage is used.

Most other conditions

1.5 to 5mg daily for one to three weeks, then reducing to the minimum effective dosage. Larger doses may be needed for mixed connective tissue diseases and ulcerative colitis.

Children

Fractions of the adult dosage may be used (e.g. 75% at 12 years, 50% at 7 years and 25% at 1 year) but clinical factors must be given due weight (see "Special Warnings and Special Precautions for Use").

4.3 Contraindications

Systemic infections, unless specific anti-infective therapy is employed. Hypersensitivity to any components of the tablet.

4.4 Special warnings and precautions for use

A patient information leaflet should be supplied with this product.

Undesirable effects may be minimised by using the lowest effective dose for the minimum period, and by administering the daily requirement as a single morning dose, or whenever possible as a single morning dose on alternate days. Frequent patient review is required to appropriately titrate the dose against disease activity (see "Posology and Method of Administration").

Caution is advised with the use of corticosteroids in patients who have suffered a recent myocardial infarction because of the risk of myocardial rupture.

Caution is advised on the use of corticosteroids in patients with hypothyroidism or myasthenia gravis.

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 (or parents of children) 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.

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

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.

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.

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.

Adrenal suppression

Adrenal cortical atrophy develops during prolonged therapy and may persist for years after stopping treatment.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 1mg betamethasone or equivalent) for greater than 3 weeks, withdrawal should not be abrupt.

How dose reduction should be carried out depends largely on whether the disease is likely to relapse as a dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids but there is uncertainty about hypothalamic-pituitary-adrenal (HPA) suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose equivalent to 1mg betamethasone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks, is appropriate if it is considered that the disease is unlikely to relapse. Abrupt withdrawal of doses of up to 6mg daily of betamethasone or equivalent for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be **considered** even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who have reasons for adrenocortical insufficiency other than exogenous corticosteroids therapy.
- Patients receiving doses of systemic corticosteroid greater than 6mg daily of betamethasone (or equivalent).
- Patients repeatedly taking doses in the evening.

During prolonged therapy any intercurrent illness, trauma or surgical procedure will require a temporary increase in dosage; if corticosteroids have been stopped following prolonged therapy they may need to be temporarily reintroduced.

Special precautions

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.

Patients should carry "Steroid Treatment" cards which give clear guidance on the precautions to be taken to minimize risk and which provide details of prescriber, drug, dosage and the duration of treatment.

Use in children

Caution is advised in children as they are more susceptible to systemic toxicity from betamethasone. Corticosteroids cause dose-related growth retardation in infancy, childhood and adolescence, which may be irreversible. Treatment should be limited to the minimum dosage for the shortest possible time. In order to minimize suppression of the HPA axis and growth retardation, consideration should be given to administration of a single dose on alternate days.

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 interactions

Steroids may reduce the effects of anticholinesterases in myasthenia gravis, cholecystographic x-ray media and non-steroidal anti-inflammatory agents.

Rifampicin, rifabutin, carbamazepine, phenobarbitone, phenytoin, primidone, aminoglutethimide and ephedrine enhance the metabolism of corticosteroids; thus the corticosteroid therapeutic effect may be reduced.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

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

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

The risk of hypokalaemia is increased with theophylline, ulcer healing drugs such as carbenoxolone and antifungals such as amphotericin B.

Increased toxicity may result if hypokalaemia occurs in patients on cardiac glycosides.

Ritonavir and oral contraceptives may result in increased plasma concentrations of corticosteroids.

The effect of corticosteroids may be reduced for 3-4 days after mifepristone.

The growth promoting effect of somatropin may be inhibited by corticosteroids.

An increase in the incidence of gastrointestinal bleeding may occur if NSAIDs are taken concomitantly with corticosteroids.

Corticosteroids may antagonise the effects of neuromuscular blocking drugs such as vecuronium.

Concurrent use of corticosteroids and fluoroquinolones may result in increased risk of tendon rupture.

Quetiapine may result in decreased levels of corticosteroids.

Corticosteroids may enhance the metabolism of tretinoin resulting in decreased levels of tretinoin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The ability of corticosteroids to cross the placenta varies between individual drugs; however, betamethasone readily crosses the placenta. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development.

There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate/lip in man. However, when administered for prolonged periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation.

Hypoadrenalism may, in theory, occur in the neonate following prenatal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. Hypertrophic cardiomyopathy and gastroesophageal reflux have been associated with in utero exposure to betamethasone.

As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. 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.

Betamethasone, systemically administered to a woman during pregnancy may result in a transient suppression of the foetal heart rate parameters and biophysical activities that are widely used for the assessment of foetal well – being. These characteristics can include a reduction in foetal breathing movements, body movements and heart rate.

Lactation

Corticosteroids may pass into breast milk, although no data are available for betamethasone. Infants of mothers taking high doses of systemic corticosteroids for prolonged periods may have a degree 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 potency of the drug, dosage, timing of administration and the duration of treatment. (see "Special Warnings and Special Precautions for Use").

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, nitrogen and calcium balance. Increased appetite. Hyperhydrosis. Increased high – density lipoprotein and low – density lipoprotein concentrations in the blood.

Anti-inflammatory and immunosuppressive effects

Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis (see "Special Warnings and Special Precautions for Use").

Musculoskeletal

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

Fluid and electrolyte disturbance

Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis.

Neuropsychiatric

Euphoria, psychological dependence, depression, psychosis, insomnia, and aggravation of schizophrenia. 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.

Vision, blurred (see also section 4.4)

Cardiac

Myocardial rupture following recent myocardial infarction.

Gastrointestinal

Abdominal distension, oesophageal ulceration, nausea, dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis, candidiasis.

Dermatological

Impaired healing, skin atrophy, bruising, telangiectasia, striae, acne, Stevens-Johnson syndrome.

General

Hypersensitivity including anaphylaxis has been reported. Leucocytosis. Thrombo-embolism. Malaise. Hiccups.

Withdrawal symptoms and signs

Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency; hypotension and death (see "Special Warnings and Special Precautions for Use").

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

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: H02A B01

Betamethasone is a glucocorticosteroid (which is about eight to ten times as active as prednisolone on a weight-for-weight basis) with topical anti-inflammatory activity.

5.2 Pharmacokinetic properties

The vast majority of corticosteroids, including betamethasone, are absorbed from the gastrointestinal tract.

Corticosteroids are metabolised mainly in the liver but also in the kidney, and are excreted in the urine.

Synthetic corticosteroids, such as prednisolone, have increased potency when compared to the natural corticosteroids, due to their slower metabolism and lower protein-binding affinity.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydrogen Carbonate (E500)
Sodium Acid Citrate
Saccharin Sodium
Povidone
Erythrosine (E127)
Sodium Benzoate (E211)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package to protect from light.

6.5 Nature and contents of container

The tablets are sealed into individual pockets in an aluminium/polyethylene laminate (30 micron and 38 micron respectively). The tablets are strip packed in cartons of 100.

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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Sweden

8 MARKETING AUTHORISATION NUMBER

PA1638/001/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13 August 2008

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February 2022