IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0365/066/001
Case No: 2062927

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

UCB Pharma Limited

208 Bath Road, **Slough**, **Berkshire SL1 3WE**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Betnelan 500 microgram Tablets.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **22/07/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Betnelan 500 microgram Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 micrograms (0.5 mg) betamethasone.

Excipients: contains 97mg lactose per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Small, white flat tablet engraved ‘Betnelan 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

Betamethasone is a glucocorticosteroid which is about eight to ten times as active as prednisolone on a weight-for-weight basis.

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

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 thrombocytopenia purpura; immuno-suppression in transplantation.

4.2 Posology and method of administration

The lowest dosage that will produce an acceptable result should be used; when it is possible to reduce the dosage, this must be accomplished in stages. During prolonged therapy, dosage may need to be increased temporarily during periods of stress or in exacerbation of illness *(see Special Warnings and 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 dosage 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:
A proportion of the adult dosage may be used (e.g. 75% at twelve years, 50% at seven years and 25% at one year) but clinical factors must be given due consideration *(see Special Warnings and Precautions for Use).*

4.3 Contraindications

Systemic infections, unless specific anti-infective therapy is employed. Hypersensitivity to any components of the tablet. Use in patients with peptic ulcer or acute psychosis.

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 as a single morning dose on alternate days whenever possible. 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 with hypothyroidism or myasthema gravis.

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

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.

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 re-introduced.

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 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 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 minimise 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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.

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 or 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.

4.6 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 forbetamethasone. 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 Precautions for Use).*

Blood and lymphatic system disorders: Leucocytosis

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

Endocrine disorders:
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 requirements for antidiabetic therapy. Negative protein and calcium balance. Increased appetite. Sodium and water retention, 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.

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

Vascular disorders:
Thrombo-embolism, hypertension.

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

Skin and subcutaneous tissue disorders:
Impaired healing, skin atrophy, bruising, telangiectasia, striae, acne, Stevens-Johnson syndrome.

Musculoskeletal, connective tissue disorders:
Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, proximal myopathy.

General disorders and administration site conditions:
Hypersensitivity including anaphylaxis, has been reported.

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 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 Code: H02A B01

Betamethasone is a glucocorticoid which is about eight to ten times as active as prednisolone on a weight-for-weight basis.

5.2 Pharmacokinetic properties

Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolised primarily in the liver and are then excreted by the kidneys.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Gelatin
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container to protect from light.

6.5 Nature and contents of container

Tubular glass vial with a polyurethane snap-plug closure containing 100 tablets

Tamper evident polypropylene container with a polyurethane foam wad and a low density polyethylene lid containing 500 tablets.

Not all pack sizes may be marketed.

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

UCB Pharma Limited
208 Bath Road
Slough
Berkshire
SL1 3WE
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0365/066/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1978

Date of last renewal: 13 August 2008

10 DATE OF REVISION OF THE TEXT

July 2009