1. NAME OF THE MEDICINAL PRODUCT

Betham® 2 mg, scored tablets (Betamethasone Sodium Phosphate Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of betamethasone as betamethasone sodium phosphate

Excipients with known effect:
Betham® tablets contain lactose and sucrose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Scored, Uncoated Tablet.

White to off white, round, flat bevel edged tablet having a break line on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CONDITIONS OR DISEASES:

I- COLLAGENOSIS-CONNECTIVITIS
Acute exacerbations of systemic diseases, including: systemic lupus erythematosus, vasculitis, polymyositis, visceral sarcoidosis.

II- DERMATOLOGICAL
a- severe autoimmune bullous dermatoses, in particular pemphigus and bullous pemphigoid
b- severe forms of infantile haemangioma
c- certain forms of lichen planus
d- certain forms of acute urticaria
e- severe forms of neutrophilic dermatoses

III- DIGESTIVE
a- acute exacerbations of ulcerative colitis and Crohn's disease
b- active chronic autoimmune hepatitis (with or without cirrhosis)
c- severe acute alcoholic hepatitis, histologically-proven

IV- ENDOCRINE
a- severe subacute De Quervain’s thyroiditis
b- some hypercalcemias

V- HAEMATOLOGICAL
a- severe immune thrombocytopenic purpura
b- autoimmune haemolytic anaemias
c- in combination with various chemotherapies in the treatment of lymphoid haematological malignancies
d- acquired or congenital chronic erythroblastopenia

VI- INFECTIOUS
a- tuberculous pericarditis and severe forms of life-threatening tuberculosis

b- *Pneumocystis carinii* pneumonia with severe hypoxia

VII- NEOPLASIAS
a- anti-emetic treatment during antineoplastic chemotherapy
b- oedematous and inflammatory effects associated with antineoplastic treatments (radio and chemotherapy)

VIII- NEPHROLOGY
a- nephrotic syndrome with minimal glomerular lesions
b- nephrotic syndrome with primary focal and segmental hyalinoses
c- class III and IV lupus nephropathy
d- renal granulomatous sarcoidosis
e- vasculitis with renal involvement
f- primary extracapillary glomerulonephritis

IX- NEUROLOGICAL
a- myasthenia
b- cerebral oedema due to tumour
c- chronic, idiopathic, inflammatory polyradiculoneuropathy
d- infantile spasm (West syndrome) / Lennox-Gastaut syndrome
e- relapsing multiple sclerosis, as a relay to intravenous corticosteroid therapy

X- OPHTHALMOLOGICAL
a- severe anterior and posterior uveitis
b- oedematous exophthalmos
c- certain forms of optic neuropathies, as a relay to intravenous corticosteroid therapy (in this indication, the oral route is not recommended as a first-line treatment)

XI- ENT
a- certain serous otitis
b- nasosinus polyposis
c- certain forms of acute or chronic sinusitis
d- seasonal allergic rhinitis as short-term treatment
e- acute subglottic laryngitis (stridulous laryngitis) in children

XII- RESPIRATORY
a- persistent asthma, preferably in a short course of treatment, if high-dose inhaled therapy has failed
b- asthma exacerbations, especially severe acute asthma
c- chronic obstructive pulmonary disease in assessing the reversibility of the obstructive syndrome
d- progressive sarcoidosis
e- diffuse interstitial pulmonary fibrosis

XIII- RHEUMATIC
a- rheumatoid arthritis and certain forms of polyarthritis
b- rhizomelic pseudopolyarthritis and Horton's disease
c- acute articular rheumatism
d- severe and rebellious cervicobrachial neuralgia

XIV- ORGAN AND HAEMATOPOIETIC ALLOGENIC STEM CELL TRANSPLANTATION
a- prophylaxis or treatment of transplant rejection
b- prophylaxis or treatment of graft-versus-host disease

4.2 Posology and method of administration

Oral route.

- Anti-inflammatory equivalence (equipotence) for 5 mg prednisone: 0.75 mg betamethasone.
- The tablets can be swallowed whole with a little water, preferably during meals.

FOR ADULT USE ONLY

Betham® 2 mg is particularly suitable for initial high-dose treatment or short-term treatment requiring medium to high doses in adults.
For maintenance treatment, more appropriate dosage forms are available.
For children, more appropriate dosage and pharmaceutical forms are available.
The dosage varies according to the diagnosis, severity of the condition, prognosis, patient response and tolerance to treatment.
Initial treatment: 0.05 mg to 0.2 mg/kg/day (i.e., 0.35 mg to 1.2 mg/kg/day prednisone equivalent).
As general guidance only: 1.5 to 6 tablets in a 60 kg adult.
In severe inflammatory disease, the dosage varies from 0.1 to 0.2 mg/kg/day of betamethasone (0.75 mg/kg/day to 1.2 mg/kg/day prednisone equivalent).
As general guidance only: 3 to 6 tablets per day for a 60 kg adult.
In very exceptional situations higher doses may be required.

IN GENERAL

Treatment at the "initial treatment dose" should be continued until the disease is under sustained control.
Tapering down of dose must be slow. Weaning is the goal. Sometimes, as a compromise, it might be necessary to continue with a maintenance dose (lowest effective dose).
For prolonged treatment at high doses, the first doses can be divided into two daily doses. Thereafter, the daily dose can be administered as a single dose, preferably in the morning with a meal.

Discontinuation of treatment

The rate of dose reduction depends mainly on the duration of treatment, the starting dose and the disease.
Treatment causes an interruption of ACTH and cortisol secretions, sometimes associated with permanent adrenal insufficiency. During dose reduction, tapering down should be in gradual stages, because of the risk of relapse: reduction of 10% every 8 to 15 days on average.
For short courses of treatment of less than 10 days, there is no need to taper off the treatment.
During dose reduction (after long-term treatment): at a dosage of 5-7 mg prednisone equivalent, when the causative disease no longer requires corticosteroid therapy, it is desirable to replace the synthetic corticosteroid with 20 mg/day hydrocortisone until corticotropic function is restored.
If corticosteroid therapy is to be maintained at a dose of less than 5 mg prednisone equivalent per day, a small dose of hydrocortisone can be added to achieve a hydrocortisone equivalent of 20-30 mg per day. When the patient only takes hydrocortisone, the corticotropic axis can be tested with endocrine tests. These tests alone do not eliminate the possibility of adrenal insufficiency occurring during stress.
While taking hydrocortisone, or even after discontinuation, the patient should be warned of the need to increase the usual dosage or to restart replacement therapy (e.g., 100 mg intramuscular hydrocortisone every 6-8 hours) in case of stress: surgery, trauma, infection.

4.3 Contraindications

This medicinal product is generally contraindicated in the following situations (there is, however, no absolute contraindication for a life-saving corticosteroid therapy):

- Any infectious condition other than the specified indications (see section 4.1),
- Certain evolving virus diseases (in particular, hepatitis, herpes, chickenpox, shingles),
- Psychotic states not yet controlled by treatment,
- Live vaccines,
- Hypersensitivity to any of the ingredients.

This medicinal product is generally not recommended in combination with non-antiarrhythmic drugs that can cause torsades de pointes (see section 4.5).

4.4 Special warnings and precautions for use

Special warnings

- Pheochromocytoma crisis, which may 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.

- In cases of peptic ulcer disease, corticosteroid therapy is not contraindicated if anti-ulcer treatment is associated.

- If there is a history of ulcer disease, corticosteroid therapy may be prescribed, under clinical monitoring and, if necessary, after fibroscopy.

- Corticosteroid therapy can lead to a variety of infectious complications due to bacteria, yeast and parasites. The occurrence of malignant anguillulosis is a significant risk.

  All patients living or having spent time in endemic areas (tropical or subtropical regions, southern Europe) should undergo parasitological examination of the stools and systematic eradication treatment before corticosteroid therapy.

  Signs of a developing infection may be masked by corticosteroid therapy.

  It is therefore important, before starting treatment, to rule out any possibility of visceral foci, in particular tuberculosis, and to monitor the appearance of infectious pathologies during treatment.

  In case of old tuberculosis, prophylactic anti-tuberculosis treatment is necessary if there are significant radiological sequelae and if it cannot be established that a well-conducted 6-month course of rifampicin has been administered.

- The use of corticosteroids requires particularly appropriate monitoring, especially in elderly patients and in cases of ulcerative colitis (risk of perforation), recent intestinal anastomoses, renal failure, hepatic insufficiency, osteoporosis, myasthenia gravis.

Precautions for use

- *In case of long-term treatment with corticosteroids:*
  - A diet low in rapidly absorbed sugars and high in protein should be combined with the treatment, due to its hyperglycaemic effect and protein catabolism, which may lead to a negative nitrogen balance.
  - Water/sodium retention is usual, and partly responsible for a possible rise in blood pressure. Sodium intake should be reduced for daily doses above 15 or 20 mg prednisone equivalent, and moderated during long-term low-dose therapy.
  - Potassium supplementation is only justified for long-term high-dose treatments, or in case of risk of rhythm disorders or association with hypokalemic treatments.
  - The patient should be systematically supplemented with calcium and vitamin D.
  - When corticosteroid therapy is indispensable, diabetes and high blood pressure are not contraindications, but the treatment may cause an imbalance. Management of these conditions should be reassessed.

- Patients should avoid contact with individuals with chickenpox or measles.

- Athletes should be aware that this medicinal product contains an active ingredient that can induce a positive reaction in tests carried out during anti-doping controls.

Visual disturbances may occur with systemic or local corticosteroid therapy (including nasal, inhaled and intraocular). If blurred vision or any other visual symptoms occur during corticosteroid therapy, an ophthalmologic examination is needed to check for visual disorders such as cataract, glaucoma, or other rarer lesions such as central serous chorioretinopathy, which have been described in association with local or systemic administration of corticosteroids.

Betham® contains lactose and sucrose
Patients with intolerance to galactose, total lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases) should not take this medicine.

Betham® contains sodium
Betham® 2 mg, scored tablet contains less than 1 mmol (23 mg) of sodium per tablet, i.e., it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Inadvisable combinations

+**Drugs known to produce torsades de pointes** (astemizole, bepridil, erythromycin IV, halofantrine, pentamidine, sparfloxacin, sultopride, terfenadine, vincamine)
In case of hypokalaemia, use products that do not have the disadvantage of causing torsades de pointes.
+ CYP3A inhibitors
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.

Combinations subject to precautions for use

+ Systemic acetylsalicylic acid and, by extrapolation, other salicylates
Decrease in blood salicylate levels during corticosteroid treatment and risk of salicylate overdose after discontinuation, due to increased elimination of salicylates by corticosteroids.
Adjust salicylate doses during combination and after discontinuation of corticosteroids.
+**Anti-arrhythmic drugs known to produce torsades de pointes** (amiodarone, bretylium, disopyramide,
quinidines, sotalol).
Hypokalaemia is a contributing factor to bradycardia and a pre-existing prolonged QT interval.
Prevent hypokalaemia, and correct it if necessary; monitor QT interval. In case of torsade, do not administer antiarrhythmic drugs (electrosystolic stimulation).
+ Oral anticoagulants
Possible impact of corticosteroid therapy on the metabolism of oral anticoagulants and on coagulation factors.
At high doses or with a treatment duration of more than 10 days, there is an increased risk of bleeding specific to corticosteroid therapy (gastrointestinal mucosa, vascular fragility).
Patients taking corticosteroids associated with oral anticoagulants should be closely monitored (biological investigations on day 8, then every 2 weeks during treatment and after treatment discontinuation).
+**Other hypokalemic drugs** (hypokalemic diuretics, alone or in combination, stimulant laxatives, amphotericin B IV).

Increased risk of hypokalaemia due to additive effect.
Monitor potassium levels, correct, if necessary, especially in the case of digitalis therapy.
+ Digitalis
Hypokalaemia may increase the toxic effects of digitalis.
Monitor potassium levels, correct if necessary, and possibly conduct an ECG.
+ Parenteral heparins
Heparin increases the risk of bleeding specific to corticosteroid therapy at high doses or with treatment for more than 10 days (gastrointestinal mucosa, vascular fragility).
The association must be justified, and monitoring must be strengthened.
+**Enzyme inducers**: carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampicin.
Decreased plasma levels and effectiveness of corticosteroids due to increased hepatic metabolism. The consequences are particularly important in the case of Addisonian patients and in the case of transplant patients.
Clinical and biological surveillance, adjustment of corticosteroid dosage during association and after discontinuation of the enzyme inducer.
+ Insulin, metformin, hypoglycaemic sulphonamides
Increased blood sugar levels, sometimes with ketosis (reduced carbohydrate tolerance due to corticosteroids).
Patients must be warned and increase blood and urine self-monitoring, especially at the start of the treatment.
If necessary, adjust the dosage of antidiabetic drugs during and after discontinuation of corticosteroid therapy.
+ Isoniazid (described for prednisolone)
May decrease isoniazid serum levels. Suggested mechanism: increased hepatic metabolism of isoniazid and decreased metabolism of glucocorticoids.
Clinical and biological monitoring.
+**Gastrointestinal topicals**: salts, oxides and hydroxides of magnesium, aluminium and calcium (described for prednisolone, dexamethasone).
Decreased digestive absorption of glucocorticoids.
Gastrointestinal topicals should be taken separately from glucocorticoids (with an interval between treatments of at least 2 hours, if possible).

Associations to be taken into account

+ Anti-hypertensives
Decreased antihypertensive effect (water/sodium retention due to corticosteroids).
+ Interferon alpha
Risk of inhibition of the action of interferon.
+ Live attenuated vaccines
Risk of generalised disease, possibly fatal. This risk is increased in patients immunocompromised by the underlying disease.
Use an inactivated vaccine if available (poliomyelitis).

4.6 Pregnancy and lactation

Pregnancy
Animal experiments show a teratogenic effect that varies according to the species.
In humans, there is placental transfer. However, epidemiological studies have found no risk of malformations associated with the intake of corticosteroids in the first trimester of pregnancy.
In the case of chronic diseases requiring treatment throughout the pregnancy, a slight intrauterine growth retardation is possible. Neonatal adrenal insufficiency has been observed exceptionally after high-dose corticosteroid therapy.
A period of biological and clinical monitoring (weight, diuresis) of the new-born is justified.
Therefore, corticosteroids can be prescribed during pregnancy, if essential.

Breastfeeding
Breastfeeding is not recommended in case of long-term high-dose treatment.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Undesirable effects are especially to be feared at high doses or in the case of prolonged treatment over several months

- Fluid and electrolyte disorders: hypokalaemia, metabolic alkalosis, water/sodium retention, hypertension, congestive heart failure.
- Endocrine and metabolism disorders: iatrogenic Cushing's syndrome, lack of ACTH secretion, adrenal cortical atrophy, which may be permanent, decreased tolerance to glucose, manifestation of latent diabetes mellitus, growth suppression in children, menstrual irregularities.
- Musculoskeletal disorders: muscle atrophy preceded by muscular weakness (increased protein catabolism), osteoporosis, pathological fractures, in particular vertebral compression fractures, aseptic osteonecrosis of the femoral head.
- Gastrointestinal disorders: hiccups, peptic ulcers, small intestine ulceration, perforations and gastrointestinal bleeding, and acute pancreatitis have been reported, especially in children.
- Skin disorders: acne, purpura, bruising, hypertrichosis, impaired wound healing and angioedema.
- Nervous system and psychiatric disorders:
    - common: euphoria, insomnia, excitation;
    - rare: manic episodes, confusional or confused-dreamlike states, convulsions (systemic or intrathecal route).
    - depression on withdrawal of treatment.
- Eye disorders: some forms of glaucoma and cataract; blurred vision (see also section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system.

4.9 Overdose

Treatment of acute overdose includes gastric lavage and induction of emesis, with symptomatic treatment instituted as necessary

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Betamethasone is a synthetic analog of prednisolone which is more potent milligram per milligram than hydrocortisone.
Corticosteroids have multiple actions which produce anti-inflammatory effects and result in their widespread use for treating diseases such as asthma. Historically, glucocorticoids were thought to decrease inflammation by stabilizing the lysosomes in neutrophils which prevented degranulation and the resulting inflammatory response. Additional research demonstrated that glucocorticoids also induce the anti-inflammatory protein, lipocortin. This protein inhibits the enzyme phospholipase A2

which inhibits synthesis of prostaglandins and lipoxygenase products. Corticosteroids also bind to glucocorticoid receptors (GRs) located in the cytoplasm. After binding occurs, the activated GR moves from the cytoplasm to the nucleus where upregulation of anti-inflammatory genes (eg, lipocortin, neutral endopeptidase, inhibitors of plasminogen activator) occurs. This effect results from binding of the GRs to glucocorticoid response elements (GREs). Corticosteroids also decrease the stability of selected messenger RNA molecules which alter gene transcription. Genes affected by this action include those involved in synthesis of collagenase, elastase, plasminogen activator, nitric oxide synthase, cyclooxygenase type II, cytokines, and chemokines. During allergic reactions, four types of cytokines are believed to induce allergic cell
recruitment. The cytokines, tumor necrosis factor-alpha and interleukin (IL)-1, non-specifically activate the endothelium which promotes recruitment of neutrophils, eosinophils, mononuclear cells, and basophils. Selective activation of the endothelium results from release of the cytokines, IL-4 and IL-13. These cytokines promote expression of vascular cell adhesion molecule-1 and binding of basophils, eosinophils, monocytes, and lymphocytes which have the leukocyte counter ligand very late activation antigen-4. The third class of cytokines, IL-3, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon gamma, cause prolonged eosinophil survival, increased adhesion molecule expression, and increased eosinophil degranulation and movement across the endothelial barrier. The last class of cytokines, the chemokines, have chemotactic properties which induce cell migration and activate selected cell types. Corticosteroids are effective inhibitors of the described cytokines and thus reduce the inflammatory response elicited by these cytokines.

5.2 Pharmacokinetic properties

Corticosteroids are, in general, readily absorbed from the gastrointestinal tract. They are also absorbed when given locally. After topical use, particularly under an occlusive dressing or when the skin is broken, or use rectally as an enema, sufficient corticosteroid may be absorbed to give systemic effects; this is also a possibility with other local routes such as inhalation. Water-soluble forms of corticosteroids are given by intravenous injection for a rapid response; more prolonged effects are achieved using lipid-soluble forms of corticosteroids by intramuscular injection.
Corticosteroids are rapidly distributed to all body tissues. They cross the placenta to varying degrees and Inay be distributed in small amounts into breast milk. Most corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and less so to albumin. The corticosteroid-binding globulin (transcortin) bas high affinity but low binding capacity, while albumin has low affinity but large binding capacity. The synthetic corticosteroids are less extensively protein bound than hydrocortisone (cortisol) . They also tend to have longer half-lives. Corticosteroids are metabolised mainly in the liver but also in other tissues and are excreted in the urine. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate, Sodium Starch Glycolate, Sucrose, Sodium lauryl sulphate, Magnesium Stearate.

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

Tablets: 24 months.

6.4 Special precautions for storage

Store at a temperature below 30°C.

6.5 Nature and contents of container

Betham® 2 mg, scored tablets: white, round, scored tablets, in white opaque PVC-PVDC/Aluminium 10 tablets blister packs. Each box contains 2x10 tablet blister packs.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Expharlab Ltd.
387, Agege Motor Road,
Mushin. Lagos.

8. DRUG PRODUCT MANUFACTURER

Gracure Pharmaceuticals Ltd.,
E-1105, RIICO Industrial Area
Phase III, Bhiwadi, Alwar (Rajasthan), India

9. NAFDAC REGISTRATION NUMBER