1. Name of the medicinal product: BETALARN (Betamethasone Tablets BP 0.5 mg)

2. Qualitative and quantitative composition:
Each Uncoated Tablet Contains:
Betamethasone BP 0.5 mg
Excipients q.s.

Excipients with known effect: Lactose Monohydrate, Sodium Lauryl Sulfate.

3. Pharmaceutical form: Uncoated tablet

Description: White coloured, round shaped, flat, uncoated tablet, breakline on one side, plain on other side.

4. Clinical Particulars
4.1 Therapeutic indications
BETALARN (Betamethasone Tablets BP) are indicated for following conditions:
- 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 (autoimmune), acute and lymphatic leukaemia, malignant lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura;
- Immunosuppression in transplantation.

4.2 Posology and method of administration
Posology
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.
Adults:
The dose used will depend on the disease, its severity and the clinical response obtained. The following regimens are for guidance only. Divided dosage is usually employed.
Short term treatment:
2-3mg daily for the first few days, then reducing the daily dose by 250 or 500mcg (0.25 or 0.5mg) every two to five days, depending upon the response.
Rheumatoid arthritis:
500mcg (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.

Paediatric population:

A proportion 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.

Method of administration:

For oral use.

4.3 Contraindications

BETALARN (Betamethasone Tablets BP) are contraindicated in :

Hypersensitivity to the active substance or to any of the excipients.

Systemic infections, unless specific anti-infective therapy is employed.

4.4 Special warnings and precautions for use

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.

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.

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 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 treatment 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 when 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.
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.
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.
Paediatric population
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.
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
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), antihypertensives 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 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.

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

Concomitant use of betamethasone with quetiapine may result in the increased metabolism of quetiapine and, depending on the clinical response, a higher dose of quetiapine may need to be considered.

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.

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

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 intrauterine 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. Myocardial hypertrophy and gastroesophageal reflux have been reported in association 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.

Fertility

There are no data in humans to evaluate the effect of corticosteroids on fertility.

4.7 Effects on ability to drive and use machines

Betamethasone Tablets are unlikely to affect your ability to drive or use machines.

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.

Not known: frequency cannot be estimated from the available data.

System organ class	Frequency	Undesirable effects
Infections and infestations	Not known	Increased susceptibility to and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis
Endocrine disorders	Not known	Suppression of the HPA axis, growth suppression in infancy, childhood and adolescence, menstrual irregularity and amenorrhoea.
Metabolism and nutrition disorders	Not known	Cushingoid facies, hirsutism, weight gain, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy*
Psychiatric disorders	Common	A wide range of psychiatric reactions**
Eye disorders	Not known	Increased intra-ocular pressure, glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning, exacerbation of ophthalmic viral or fungal diseases Vision, blurred
Cardiac disorders	Not known	Myocardial rupture following recent myocardial infarction
Gastrointestinal disorders	Not known	Abdominal distension, oesophageal ulceration, nausea, dyspepsia, peptic ulceration with perforation and haemorrhage, acute pancreatitis, candidiasis
Skin and subcutaneous tissue disorders	Not known	Impaired healing, skin atrophy, bruising, telangiectasia, striae, acne, Stevens-Johnson syndrome.
Musculoskeletal and connective tissue disorders	Not known	Osteoporosis, vertebral and long bone fractures, avascular osteonecrosis, tendon rupture, proximal myopathy
General disorders and administration site conditions	Not known	Hypersensitivity including anaphylaxis has been reported. Leucocytosis. Thrombo-embolism. Malaise. Hiccups

* Negative protein, nitrogen and calcium balance. Increased appetite. Hyperhidrosis. Increased high - density lipoprotein and low – density lipoprotein concentrations in the blood. Fluid and electrolyte disturbance (Sodium and water retention, hypertension, potassium loss, hypokalaemic alkalosis).
** 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 and 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.
Withdrawal symptoms and signs
Too rapid 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
The following effects have been reported in cases of overdosage:
Symptoms
Symptoms of corticosteroid overdose can include:
- Altered mental status with agitation (psychosis)
- Burning or itching skin
- Convulsions
- Deafness
- Depression
- Dry skin
- High blood pressure
- Increased infection risk
- Muscle weakness
- Nausea and vomiting
- Nervousness
- Sleepiness
- Stopping of menstrual cycle
- Swelling in lower legs, ankles, or feet

Treatment may include:
- Activated charcoal
- Breathing support, which may include oxygen or a ventilator (tube through the mouth into the lungs and breathing machine
- Intravenous fluids (IV, given through a vein)
- Laxatives
- Medicine to treat symptoms
- Skin and eye washing if the product touched these tissues and they are irritated or swollen.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids for systemic use, plain, Glucocorticoids,
ATC code: H02A B01

Betamethasone is an active corticosteroid with topical anti-inflammatory activity. Betamethasone is a synthetic analog of prednisolone which is more potent milligram per milligram than hydrocortisone.

Mechanism of action:

Corticosteroids 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. Corticosteroids are effective inhibitors of the described cytokines and thus reduce the inflammatory response elicited by these cytokines.

5.2 Pharmacokinetic properties

Absorption and Bioavailability

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

Distribution

Betamethasone binds to serum albumin and corticosteroid-binding globulin.

Metabolism

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.

Elimination

Corticosteroids are eliminated predominantly in the urine, mainly as inactive metabolites.

Special Population

Data not available.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6. Pharmaceutical particulars

6.1 List of excipients

Maize Starch, Lactose Monohydrate, Calcium Hydrogen Phosphate Dihydrate, Microcrystalline Cellulose, Sodium Lauryl Sulfate, Magnesium Stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30°C in a dry and cool place. Protect from direct sunlight.
Keep all medicines out of reach of children.
Read leaflet carefully before use.

6.5 Nature and contents of container
Primary packing: 10 Tablets in a Strip.
Secondary packing: 50 Strips are packed in a carton along with leaflet.

6.6 Special precautions for disposal and other handling
None

7. Applicant / Manufacturer
Applicant

Applicant name and address	**M/s. BARNAETO PHARMA LTD.** No.31, Turner Street, Mosefejo B/Stop, Amukoko, Lagos State
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Manufacturer

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