1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of drug product
NAFROBACT A CREAM
(BETAMETHASONE, DIPROPIONATE, CLOTRIMAZOLE & NEOMYCIN SULPHATE CREAM)

1.1 (Trade) name of product
NAFROBACT A CREAM

1.2 Strength

NAFROBACT A CREAM

Composition:

Each Gram Contains:

Betamethasone Dipropionate USP

Equivalent to Betamethasone…..... 0.05% w/w

Clotrimazole USP .....1.0% w/w

Neomycin Sulphate USP

Equivalent to Neomycin Base..... 0.5% w/w

Cream base..... Q.S.

Preservative

Chlorocresol USP.....0.1% w/w

1.3 Pharmaceutical Dosage Form

Semi solid external preparation

NAFROBACT A CREAM
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2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Composition:

Each Gram Contains:

Betamethasone Dipropionate USP
Equivalent to Betamethasone…..... 0.05% w/w
Clotrimazole USP .....1.0% w/w
Neomycin Sulphate USP
Equivalent to Neomycin Base..... 0.5% w/w
Cream base..... Q.S.
Preservative
Chlorocresol USP.....0.1% w/w

2.2 Quantitative Declaration

Batch Formula:

Batch Size: 750 Kg

Sr. No	Ingredients	Grade	Rationale	Label Claim	Overages (%)	Quantity per Unit (mg)	Quantity per Batch (Actual-Kg)
1.	Clotrimazole	USP	Active	1.0% w/w	-----	10.0	7.500
2.	Betamethasone Dipropionate eq. to Betamethasone	USP	Active	0.05%w/w	-----	0.643	0.375
3.	Neomycin Sulphate eq. to Neomycin Base	USP	Active	0.5% w/w	-----	5.40	3.750
4.	Chlorocresol	USP	Preservative	0.1% w/w	-----	1.0	0.750
5.	Cetostearyl Alcohol	BP	Emulsion Base	-----	-----	60.0	45.00

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6.	Cetomacragol 1000	BP	Emulsifier	-----	-----	18.0	13.50
7.	Light Liquid Paraffin	BP	Vehicle			40.0	30.00
8	White Soft Paraffin	BP	Emulsion Base	-----	-----	100.0	75.00
9.	B.H.T.	BP	Antioxidant	-----	-----	0.196	0.147
10.	Disodium EDTA	BP	Chelating Agent	-----	-----	0.611	0.458
11.	Sodium Dihydrogen Phosphate	BP	Alkalizing Agent	-----	-----	3.028	2.271
12.	Propylene Glycol	BP	Solvent	-----	-----	80.0	60.00
13	Purified Water	BP/IH	Vehicle	-----	-----	q. s.	q. s.

NAFROBACT A CREAM
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3. PHARMACEUTICAL DOSAGE FORM

Topical Cream. A white coloured Homogenous cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Betamethasone/Neomycin skin preparations are indicated for the treatment of the following conditions where secondary bacterial infection is present, suspected, or likely to occur: eczema in adults and children (aged 2 years and over), including atopic and discoid eczemas; prurigo nodularis; psoriasis (excluding widespread plaque psoriasis); neurodermatoses including lichen simplex and lichen planus; seborrhoeic dermatitis; contact sensitivity reactions; insect bite reactions; and anal and genital intertrigo.

For the treatment of:

i. All dermatomycoses due to moulds and other fungi (e.g. *Trichophyton* species)

ii. All dermatomycoses due to yeasts (*Candida* species). These include ringworm (tinea) infections (e.g. athlete's foot), paronychia, pityriasisversicolor, erythrasma and intertrigo.

iii. Skin diseases showing secondary infection with these fungi.

iv. Candidal nappy rash, vulvitis and balanitis.

4.2 Posology and Method of Administration

The cream is especially appropriate for moist or weeping surfaces, and the ointment for dry lichenified or scaly lesions, but this is not invariably so.

In adults, in the more resistant lesions, such as the thickened plaques of psoriasis on elbows and knees, the effects of this medicinal product can be enhanced, if necessary, by occluding the treatment area with polythene film. Overnight occlusion only is usually adequate to bring about a satisfactory response in such lesions, thereafter improvement can usually be maintained by regular application without occlusion.

Treatment should not be continued for more than 7 days without medical supervision.

Adults and children aged 2 years and over:

A small quantity should be applied to the affected area two or three times daily until improvement occurs. It may then be possible to maintain improvement by applying once a day or even less often.

Betamethasone/Neomycin skin preparations are suitable for use in children (2 years and over) at the same dose as adults. When used in children, courses should be limited to 5 days, if possible.

A possibility of increased absorption exists in very young children, thus this medicinal product is not recommended for use in neonates and infants younger than 2 years of age (see section 4.3 and section 4.4).

Dosage in renal impairment:

Dosage should be reduced in patients with reduced renal function (see section 4.4).

Elderly:

Betamethasone/Neomycin skin preparations are suitable for use in the elderly.

Caution should be exercised in cases where a decrease in renal function exists and significant systemic absorption of Neomycin sulphate may occur (see section 4.4).

For topical administration.

4.3 Contraindications

• Rosacea.

• Acne vulgaris.

• Perioral dermatitis.

• Perianal and genital pruritus.

• Primary cutaneous viral infections (e.g. herpes simplex, chickenpox).

• Hypersensitivity to any component of the preparation.

• Use is not indicated in the treatment of primary infected skin lesions caused by infection with fungi or bacteria; primary or secondary infections due to yeast; or secondary infections due to Pseudomonas or Proteus species.

• Dermatoses in children under 2 years of age, including dermatitis and napkin eruptions. A possibility of increased absorption exists in very young children thus this medicinal product is not recommended for use in neonates and infants (up to 2 years). In neonates and infants, absorption by immature skin may be enhanced, and renal function may be immature.

• Preparations containing Neomycin should not be used for the treatment of otitis externa when the ear drum is perforated, because of the risk of ototoxicity.

• Due to the known ototoxic and nephrotoxic potential of Neomycin sulphate, the use of Betamethasone/Neomycin skin preparations in large quantities or on large areas for prolonged periods of time is not recommended in circumstances where significant systemic absorption may occur.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Do not use the cream to treat nail or scalp infections.

4.4 Special Warnings and Precautions for Use

Long-term continuous topical therapy should be avoided where possible, particularly in infants and children, as adrenal suppression, with or without clinical features of Cushing's syndrome, can occur even without occlusion. In this situation, topical steroids should be discontinued gradually under medical supervision because of the risk of adrenal insufficiency (see section 4.8 and section 4.9).

If infection persists, systemic chemotherapy is required.

Withdraw topical corticosteroid if there is a spread of infection.

Bacterial infection is encouraged by the warm, moist conditions induced by occlusive dressings, and the skin should be cleansed before a fresh dressing is applied.

Avoid prolonged application to the face. The face, more than other areas of the body, may exhibit atrophic changes after prolonged treatment with potent topical corticosteroids. This must be borne in mind when treating such conditions as psoriasis, discoid lupus erythematosus and severe eczema.

If applied to the eyelids, care is needed to ensure that the preparation does not enter the eye, as glaucoma might result. If Betamethasone/Neomycin Cream does enter the eye, the affected eye should be bathed in copious amounts of water.

Topical corticosteroids may be hazardous in psoriasis for a number of reasons including rebound relapses, development of tolerance, risk of generalisedpustular psoriasis and development of local or systemic toxicity due to impaired barrier function of the skin. If used in psoriasis careful patient supervision is important.

Extended or recurrent application may increase the risk of contact sensitisation.

Extension of infection may occur due to the masking effect of the steroid.

Following significant systemic absorption, aminoglycosides such as Neomycin can cause irreversible ototoxicity; and Neomycin has nephrotoxic potential.

In renal impairment the plasma clearance of Neomycin is reduced (see Dosage in renal impairment, section 4.2).

Products which contain antimicrobial agents should not be diluted.

This product contains cetostearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

Following significant systemic absorption, Neomycin sulphate can intensify and prolong the respiratory depressant effects of neuromuscular blocking agents.
Laboratory tests have suggested that, when used together, this product may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to use alternative precautions for at least five days after using this product.

4.6 Fertility, pregnancy and lactation

There is little information to demonstrate the possible effect of topically applied Neomycin in pregnancy and lactation. However, Neomycin present in maternal blood can cross the placenta and may give rise to a theoretical risk of foetal toxicity, thus use of this medicinal product is not recommended in pregnancy or lactation.

Pregnancy:

There is a limited amount of data from the use of Clotrimazole in pregnant women. Animal studies with Clotrimazole have shown reproductive toxicity at high oral doses (see section 5.3). At the low systemic exposures of Clotrimazole following topical treatment, harmful effects with respect to reproductive toxicity are not predicted. Clotrimazole can be used during pregnancy but only under the supervision of a physician or midwife.

Lactation:

Available pharmacodynamic/toxicological data in animals have shown excretion of Clotrimazole/metabolites in milk after intravenous administration (see section 5.3). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from clotrimazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility:

No human studies of the effects of clotrimazole on fertility have been performed; however, animal studies have not demonstrated any effects of the drug on fertility.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Prolonged and intensive treatment with highly active corticosteroid preparations may cause local atrophic changes in the skin such as thinning, striae, and dilatation of the superficial blood vessels, particularly when occlusive dressings are used or when skin folds are involved.

As with other topical corticosteroids, prolonged use of large amounts or treatment of extensive areas can result in sufficient systemic absorption to produce suppression of the HPA axis and the clinical

features of Cushing's syndrome (see section 4.4). These effects are more likely to occur in infants and children, and if occlusive dressings are used. In infants the napkin may act as an occlusive dressing.

In rare instances, treatment of psoriasis with corticosteroids (or its withdrawal) is thought to have provoked the pustular form of the disease (see section 4.4).

There are reports of local skin burning, pruritus, pigmentation changes, allergic contact dermatitis and hypertrichosis with topical steroids.

Betamethasone/Neomycin skin preparations are usually well tolerated, but if signs of hypersensitivity appear, application should be stopped immediately.

Exacerbation of symptoms may occur.

As the listed undesirable effects are based on spontaneous reports, assigning an accurate frequency of occurrence for each is not possible.

Immune system disorders: allergic reaction (syncope, hypotension, dyspnoea, urticaria)

Skin and subcutaneous tissue disorders: blisters, discomfort/pain, oedema, erythema, irritation, peeling/exfoliation, pruritus, rash, stinging/burning.

4.9 Overdose

Acute overdosage is very unlikely to occur. However, in the case of chronic overdosage or misuse the features of Cushing's syndrome may appear and in this situation topical steroids should be discontinued gradually under medical supervision (see Section 4.4 Special Warnings and Precautions for Use).

Also, consideration should be given to significant systemic absorption of Neomycin sulphate (see 4.4 Special Warnings and Precautions for Use). If this is suspected, use of the product should be stopped and the patient's general status, hearing acuity, renal and neuromuscular functions should be monitored.

Blood levels of Neomycin sulphate should also be determined. Haemodialysis may reduce the serum level of Neomycin sulphate.

No risk of acute intoxication is seen as it is unlikely to occur following a single dermal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion. There is no specific antidote.

However, in the event of accidental oral ingestion, routine measures such as gastric lavage should be performed only if clinical symptoms of overdose become apparent (e.g. dizziness, nausea or vomiting). Gastric lavage should be carried out only if the airway can be protected adequately.

5. Pharmacological properties

5.1 Pharmacodynamic property

Pharmacotherapeutic group: Antifungals for topical use – imidazole and triazole derivatives

ATC code: D01A C01

Mechanism of Action

Clotrimazole acts against fungi by inhibiting ergosterol synthesis. Inhibition of ergosterol synthesis leads to structural and functional impairment of the cytoplasmic membrane.

Pharmacodynamic Effects

Clotrimazole has a broad antimycotic spectrum of action in vitro and in vivo, which includes dermatophytes, yeasts, moulds, etc. Under appropriate test conditions, the MIC values for these types of fungi are in the region of less than 0.062-8.0 µg/ml substrate.

The mode of action of clotrimazole is primarily fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection. In vitro activity is limited to proliferating fungal elements; fungal spores are only slightly sensitive.

In addition to its antimycotic action, clotrimazole also acts on gram-positive microorganisms (Streptococci / Staphylococci / Gardnerellavaginalis), and gram-negative microorganisms (Bacteroides).

In vitro clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci - with the exception of Enterococci - in concentrations of 0.5-10 µg/ml substrate.

Primarily resistant variants of sensitive fungal species are very rare; the development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions.
Betamethasone valerate is an active corticosteroid which produces a rapid response in those inflammatory dermatoses that are normally responsive to topical corticosteroid therapy, and is often effective in the less responsive conditions such as psoriasis. Neomycin sulphate is a broad spectrum, bactericidal antibiotic effective against the majority of bacteria commonly associated with skin infections.

5.2 Pharmacokinetic properties

The extent of percutaneous absorption of topical corticosteroid is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systematically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolised primarily by the liver and are then excreted by the kidneys.]

Pharmacokinetic investigations after dermal application have shown that clotrimazole is minimally absorbed from the intact or inflamed skin into the human blood circulation. The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.001 mcg/ml, suggesting that clotrimazole applied topically is unlikely to lead to measurable systemic effects or side effects.

5.3 Pre-clinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity, genotoxicity and carcinogenicity.

Clotrimazole was not teratogenic in reproductive toxicity studies in mice, rats and rabbits. In rats high oral doses were associated with maternal toxicity, embryotoxicity, reduced fetal weights and decreased pup survival.

In rats clotrimazole and/or its metabolites were secreted into milk at levels higher than in plasma by a factor of 10 to 20 at 4 hrs after administration, followed by a decline to a factor of 0.4 by 24 hrs.

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6. Pharmaceutical particulars

6.1 List of excipients

Chlorocresol

Cetostearyl Alcohol

Cetomacragol 1000

Light Liquid Paraffin

White Soft Paraffin

B.H.T.

Disodium EDTA

Sodium Dihydrogen Phosphate

Propylene Glycol

Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

36 months from the date of manufacture.

6.3 Special Precautions for Storage

Do not store above 25°C.

6.4 Nature and Contents of Container

30 gm lami tube of NAFROBACT CREAM in inner carton. Such 12 inner carton placed in outer carton

7. Marketing authorisation holder

Astamed Healthcare (I) Pvt. Ltd
Plot No. 2 & 3, Phase-II, Genesis Ind. Complex,
Kolgaon, Palghar-401404, Maharashtra, India

8. Marketing authorisation number(s)

NAFRO PHARMA NIGERIA LTD
Suite B16, Amori shopping Plaza,
113, Idimu Road, Orelope Egbeda Lagos,Nigeria

9. Date of first authorisation/renewal of the authorisation

10. Date of revision of the text