1.3.1 Summary of Product Characteristics (SmPC)

1. Name of Medicinal Product

CLOSOBEL CREAM

Betamethasone Dipropionate, Clotrimazole and Neomycin Sulphate Cream

2. Qualitative and Quantitative Composition

2.1. Qualitative declaration:

Composition of the Drug product:

Composition:

Betamethasone Dipropionate Eq. to Betamethasone USP….0.05% w/w
Clotrimazole USP…….……1.0% w/w
Neomycin Sulphate USP…….…..0.5% w/w
Preservative: Chlorocresol USP. NF…….…….….0.1% w/w
Cream base…….……Q.s

Qualitative & Quantitative Composition Formula:

Batch Size: 597 KG

Sr. No	Name of Material	Spec	Label claim	% Overage	Std. Qty (kg)	Reason for Inclusion
1	Clotrimazole	USP	1.0% w/w	5.0%	6.269	Active
2	Betamethasone Dipropionate	USP	0.05% w/w	5.0%	0.410	Active
3	Neomycin Sulphate	USP	0.5% w/w	15.0%	3.433	Active
4	Chlorocresol	USP -NF	0.1 w/w	----	0.597	Preservative
5	Cetostearyl Alcohol	BP	----	----	47.76	Emulsifier
6	Macrogol Cetostearyl Ether	BP	----	----	17.91	Emulsifier
7	Liquid Paraffin (Heavy)	BP	----	----	23.88 (23.77 Ltr)	Emollient
8	White soft paraffin	BP	----	----	71.64	Moisturizer
9	Propylene Glycol	BP	----		44.78	Humectants
10	Disodium hydrogen Phosphate Dihydrate	BP	----	----	0.597	Emulsifying agent
11	Sodium Dihydrogen Phosphate Dihydrate (Sodium Acid Phosphate)	BP	----	----	0.119	Buffering agents.
12	Disodium EDTA	BP	----	----	0.060	Stabilizer
13	Ortho Phosphoric acid	BP	----	----	0.445 (0.254 Ltr)	Surfactant

14	Purified water	BP	----	----	Q.s to 600 kg	Vehicle
Total Weight				30 g/Aluminium Tube		

Wt/ml of Heavy Liquid Paraffin BP=0.86g/ml
Wt/ml of Phosphoric Acid BP=1.75 g/ml

3. Pharmaceutical Form

Cream

A White coloured Soft cream.

4. Clinical Particulars

4.1. Therapeutic indications:

This cream combines three types of medicines: betamethasone Dipropionate, neomycin Sulphate, Clotrimazole. Each has their own function. Betamethasone Dipropionate is a strong corticosteroid. It reduces irritation and inflammation of the skin. Neomycin is an antibiotic& clotrimazole is aantifungals for topical use – imidazole and triazole derivatives. Betamethasone Dipropionate, neomycin cream& Clotrimazole cream is used to treat skin conditions including; eczema, psoriasis, severe insect bites, All dermatomycoses due to yeasts (Candida species). These include ringworm (tinea) infections (e.g. athlete's foot), paronychia, pityriasis versicolor, erythrasma intertrigo, Candidal nappy rash, vulvitis and balanitis and other types of rash. The cream will reduce swelling and protect the skin from infection.

4.2. Posology and method of administration

Apply this product thinly and carefully to the affected area(s). this should be done two or three times per day. This dose can be decreased once symptoms begin to improve.

If you have been using airtight dressings on the inflamed skin, clean the affected area before using the cream, and apply a new dressing. Remember to wash your hands after each application.

With sustained use of this medicine, there is an increased risk that an infection will become resistant to neomycin. Talk to your GP if you do not notice any improvement within a few days. This medicine should not be used for more than five days by children or on any facial skin.

You may be using other topical medicines alongside Betamethasone, neomycin & Clotrimazole cream. If this is the case, you are advised to wait at least 30 minutes between applications. This will prevent any medicine from becoming diluted.

If the feet are infected, they should be thoroughly washed and dried, especially between the toes, before applying the cream.

Treatment should be continued for at least one month for dermatophyte infections, or for at least two weeks for candidal infections.

4.3 Contraindications

Hypersensitivity to diclofenac, methyl salicylate or other components of the formulation, acetylsalicylic acid or other NSAIDs, aspirin "asthma", pregnancy (third trimester), lactation period, children below 6 years, broken skin. Do not use the cream to treat nail or scalp infections.

4.4 Special warnings and precautions for use

Local and systemic toxicity is common especially following long continued use on large areas of damaged skin and in flexures. If used on the face, courses should be limited to 5 days.

Topical corticosteroids may be hazardous in psoriasis for a number of reasons including rebound relapses following the development of tolerance, risk of generalised pustular psoriasis and local and systemic toxicity due to impaired barrier function of the skin.

Any of the side effects that are reported following systemic use of corticosteroids, including adrenal suppression, manifestation of Cushing's syndrome, hyperglycemia, and glycosuria may also occur with topical steroids, especially in infants and children.

Closobel Cream is not intended for ophthalmic use.

Visual disturbance may be reported with systemic and topical (including, intranasal, inhaled and intraocular) 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 of visual disturbances 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

• Long term continuous therapy should be avoided in all children irrespective of age.

• Closobel Cream should not be used with adhesive dressing.

• The safety and effectiveness of Closobel Cream has not been established in children below the age of12.

• If used on children, courses should be limited to 5 days.

Hypothalamic-pituitary adrenal axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestation of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestation of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilloedema.

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

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

Pregnancy:

There is a limited amount of data from the use of Closobel Cream in pregnant women. Animal studies with Closobel Cream have shown reproductive toxicity at high oral doses (see section 5.3). At the low systemic exposures of Closobel Cream following topical treatment, harmful effects with respect to reproductive toxicity are not predicted. Closobel Cream 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 Closobel Cream /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 breastfeeding or to discontinue/abstain from Closobel Cream 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 Closobel Cream 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

Adverse reactions reported for neomycin sulphateinclude: burning and stinging, maculopapular rash, oedema, paraesthesia and secondary infection.

Reported reactions to clotrimazole include erythema, stinging, blistering, peeling, oedema, pruritus, urticaria and general irritation of the skin.

Reactions to betamethasone dipropionate include: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hyperpigmentation, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae miliaria, capillary fragility (ecchymoses), blurred vision and sensitisation.

In children receiving topical corticosteroids, Hypothalamic-pituitary adrenal (HPA) axis suppression (HPA) axis suppression, Cushing's syndrome and intracranial hypertension have been reported. (See section 4.4)

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

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 favorable 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 properties

BETAMETHASONE DIPROPIONATE: ATC code

D07AC Corticosteroids, potent (group III)

Mechanism of action

Topical corticosteroids act as anti-inflammatory agents via multiple mechanisms to inhibit late phase allergic reactions including decreasing the density of mast cells, decreasing chemotaxis and activation of eosinophils, decreasing cytokine production by lymphocytes, monocytes, mast cells and eosinophils, and inhibiting the metabolism of arachidonic acid.

Pharmacodynamic effects

Topical corticosteroids have anti-inflammatory, antipruritic, and vasoconstrictive properties.

NEOMYCIN SULPHATE:

In prokaryotes, the 16S rRNA is essential for recognizing the 5' end of mRNA and hence positioning it correctly on the ribosome. The 16S rRNA has a characteristic secondary structure in which half of the nucleotides are base-paired. The 16S rRNA sequence has been highly conserved and is often used for evolutionary and species comparative analysis.

CLOTRIMAZOLE:

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 / Gardnerella vaginalis), 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.

5.2 Pharmacokinetic properties

CLOSOBEL CREAM is intended for treatment of skin conditions and is applied topically. Thus there are minimal pharmacokinetic aspects related to bioavailability at the site of action.

BETAMETHASONE DIPROPIONATE:

Absorption

Topical corticosteroids can be systemically absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusion, inflammation and/or other disease processes in the skin may also increase percutaneous absorption.

Distribution

The use of pharmacodynamic endpoints for assessing the systemic exposure of topical corticosteroids is necessary because circulating levels are well below the level of detection.

Metabolism

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. They are metabolised, primarily in the liver.

Elimination

Topical corticosteroids are excreted by the kidneys. In addition, some corticosteroids and their metabolites are also excreted in the bile.

NEOMYCIN SULPHATE:

The extent of percutaneous absorption of topical corticosteroids 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 systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the

CLOTRIMAZOLE:
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 Preclinical safety data

BETAMETHASONE DIPROPIONATE:

Reproductive toxicity

Subcutaneous administration of betamethasone valerate to mice or rats at doses ≥0.1 mg/kg/day or rabbits at doses ≥12 micrograms/kg/day during pregnancy produced foetal abnormalities including cleft palate and intrauterine growth retardation.

The effect on fertility of betamethasone valerate has not been evaluated in animals.

NEOMYCIN SULPHATE:
Neomycin sulfate is poorly absorbed from the normal gastrointestinal tract. The small absorbed fraction is rapidly distributed in the tissues and is excreted by the kidney in keeping with the degree of kidney function. The unabsorbed portion of the drug (approximately 97%) is eliminated unchanged in the feces.

CLOTRIMAZOLE:

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sr. No	Name of Material	Spec	Reason for Inclusion
1	Chlorocresol	USP	Preservative
2	Cetostearyl Alcohol	BP	Emulsifier
3	Macrogol Cetostearyl Ether	BP	Emulsifier
4	Liquid Paraffin (Heavy)	BP	Emollient
5	White soft paraffin	BP	Moisturizer
6	Propylene Glycol	BP	Humectants
7	Disodium hydrogen Phosphate Dihydrate	BP	Emulsifying agent
8	Sodium Dihydrogen Phosphate Dihydrate (Sodium Acid Phosphate)	BP	Buffering agents.
9	Disodium EDTA	BP	Stabilizer
10	Ortho Phosphoric acid	BP	Surfactant
11	Purified water	BP	Vehicle

6.2 Incompatibilities: Not Applicable

6.3 Shelf-life: 36 Months

6.4 Special precautions for storage:

Store in a cool place at or below 30°C. Protect from light.

Keep medicine out of reach of children.

6.5 Nature and contents of container:

Closobel Cream packed in a 30 gm Aluminium tube with carton& insert.

6.6 Special precautions for disposal and other handling

No special instructions for use/handling

7- Marketing Authorization Holder:

ELIONA PHARMACEUTICAL CO. LTD.,

No. 6, Akinfenwa Street, off Oshogbo Street, Ori-oke, Ogudu, Lagos, Nigeria.

8- Marketing Authorization Number (s):

Product license / registration Number (s)

9- Manufacturer Name:

GOPALDAS VISRAM AND CO LTD.

A-590/591, TTC Ind. Area, MIDC, Mahape, Navi Mumbai-400 710

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10- Date of first authorization/renewal of the authorization:

11- Date of revision of the text:
