SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Clanosten (Clotrimazole, Betamethasone Dipropionate and Neomycin Sulfate Cream)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each gram contains: -
Clotrimazole BP (1 % W/W)
Betamethasone Dipropionate Eq. to Betamethasone BP (0.05 %W/W)
Neomycin Sulphate BP (0.5 % W/W)
Cream base (- QS)
Chlorocresol BP (0.1 % W/W)

3. PHARMACEUTICAL FORM

Cream

4. Clinical particulars

4.1 Therapeutic indications

It is indicated in patients 17 years and older for the topical treatment of symptomatic inflammatory tinea pedis, tinea cruris and tinea corporis due to Epidermophyton floccosum, Trichophyton mentagrophytes, and Trichophyton rubrum. Effective treatment without the risks associated with topical corticosteroid use may be obtained using a topical antifungal agent that does not contain a corticosteroid, especially for non – inflammatory tinea infections. The efficacy of clotrimazole and betamethasone dipropionate cream for the treatment of infections caused by zoophilic dermatophytes (e.g., Microsporum canis) has not been established. Several cases of treatment failure of Clotrimazole, Betamethasone Dipropionate, and Neomycin Sulphate Cream in the treatment of infections caused by Microsporum can is have been reported.

4.2 Posology and method of administration

Posology
Adults and children over the age of 12 years.
Pediatric population

CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM is not recommended for children under the age of twelve years.

Administration: Topical

4.3 Contraindications

Contraindicated in patients who are sensitive to clotrimazole, betamethasone dipropionate, other corticosteroids or imidazoles, or to any ingredient in these preparations

4.4 Special warnings and precautions for use

Systemic absorption of topical corticosteroids can produce reversible hypothalamicpituitaryadrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Conditions which augment systemic absorption include use over large surface areas, prolonged use, and use under occlusive dressings. Use of more than one corticosteroidcontaining product at the same time may increase total systemic glucocorticoid exposure.

Patients applying CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA-axis suppression. This may be done by using the ACTH stimulation, morning plasma cortisol, and urinary free cortisol tests.
If HPA-axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids.
Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids.

In a small study, CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM was applied using large dosages, 7 g daily for 14 days (BID) to the crural area of normal adult subjects. Three of the eight normal subjects on whom CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM was applied exhibited low morning plasma cortisol levels during treatment.
One of these subjects had an abnormal Cortrosyn test. The effect on morning plasma cortisol was transient and subjects recovered one week after discontinuing dosing. In addition, two separate studies in pediatric patients demonstrated adrenal suppression as determined by cosyntropin testing.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios.

If irritation develops, CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAMs hould be discontinued and appropriate therapy instituted.

4.5 Interaction with other medicinal products and other forms of interaction

CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM may cause damage to latex contraceptives as the effectiveness of such contraceptives may be reduced. Consequently patient should be advised to use alternative precautions for at least five days after using this product.

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy Category C:There have been no teratogenic studies performed in animals or humans with the combination of clotrimazole and betamethasone dipropionate. Corticosteroids are generally teratogenic in laboratory animals when administered at relatively low dosage levels.

Studies in pregnant rats with intravaginal doses up to 100 mg/kg (15 times the maximum human dose) revealed no evidence of fetotoxicity due to clotrimazole exposure.

No increase in fetal malformations was noted in pregnant rats receiving oral (gastric tube) clotrimazole doses up to 100 mg/kg/day during gestation days 6-15. However, clotrimazole dosed at 100 mg/kg/day was embryotoxic (increased resorptions), fetotoxic (reduced fetal weights) and maternally toxic (reduced body weight gain) to rats. Clotrimazole dosed at 200 mg/kg/day (30 times the maximum human dose) was maternally lethal, and therefore fetuses were not evaluated in this group. Also in this study, doses up to 50 mg/kg/day (8 times the maximum human dose) had no adverse effects on dams or fetuses. However, in the combined fertility, teratogenicity, and postnatal development study described above, 50 mg/kg clotrimazole, was associated with reduced maternal weight gain and reduced numbers of offspring reared to 4 weeks.

Oral clotrimazole doses of 25, 50, 100, and 200 mg/kg/day (2-15 times the maximum human dose) were not teratogenic in mice. No evidence of maternal toxicity or embryotoxicity was seen in pregnant rabbits dosed orally with 60, 120, or 180 mg/kg/day (18-55 times the maximum human dose).

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. This dose is approximately one-fifth the maximum human dose. The abnormalities observed included umbilical hernias, cephalocele and cleft palates.

Betamethasone dipropionate has not been tested for teratogenic potential by the dermal route of administration. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

There are no adequate and well-controlled studies in pregnant women of the teratogenic effects of topically applied corticosteroids. Therefore, CLOTRIMAZOLE,

BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroids production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM is administered to a nursing woman.

Fertility
Not available.

4.7 Effects on ability to drive and use machines

Not available.

4.8 Undesirable effects

Adverse reactions reported for CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM in clinical trials were paresthesia in 1.9% of patients, and rash, edema, and secondary infection, each in 1% of patients. The following local adverse reactions have been reported with topical corticosteroids and may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. In the pediatric population, reported adverse events for CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM include growth retardation, benign intracranial hypertension, Cushing's syndrome (HPA-axis suppression), and local cutaneous reactions, including skin atrophy. Systemic absorption of topical corticosteroids has produced reversible hypothalamicpituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Adverse reactions reported with the use of clotrimazole are as follows: erythema, stinging, blistering, peeling, edema, pruritus, urticaria and general irritation of the skin.

4.9 Overdose

Amounts greater than 45g/week of CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM should not be used. Acute overdosage with topical application of CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM is unlikely and would not be expected to lead to life-threatening situation. CLOTRIMAZOLE, BETAMETHASONE

DIPROPIONATE & NEOMYCIN SULPHATE CREAM should not be used for longer than the prescribed time period.

Topically applied corticosteroids, such as the one contained in CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM can be absorbed in sufficient amounts to produce systemic effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM has been shown to be at least as effective as clotrimazole alone in a different cream vehicle. Use of corticosteroids in the treatment of fungal infection may lead to suppression of host inflammation leading to worsening or decreased cure rate. Milzol Plus creamhas been shown to be at least as effective as clotrimazole alone in a different cream vehicle. Use of corticosteroids in the treatment of fungal infection may lead to suppression of host inflammation leading to worsening or decreased cure rate.

Clotrimazole
Skin penetration and systemic absorption of clotrimazole following topical application of clotrimazole and betamethasone dipropionate cream have not been studied. The following information was obtained using 1% clotrimazole cream and solution formulations. Six hours after the application of radioactive clotrimazole 1% cream and 1% solution onto intact and acutely inflamed skin, the concentration of clotrimazole varied from 100 mcg/cm3 in the stratum corneum, to 0.5 to 1 mcg/cm3 in the reticular dermis, and 0.1 mcg/cm3 in the subcutis. No measurable amount of radioactivity (<0.001 mcg/mL) was found in the serum within 48 hours after application under occlusive dressing of 0.5 mL of the solution or 0.8 g of the cream. Only 0.5% or less of the applied radioactivity was excreted in the urine.

Betamethasone Dipropionate
Betamethasone dipropionate, a corticosteroid, has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Neomycin sulphate
Neomycin is a rapidly bactericidal aminoglycoside antibiotic effective against Gram positive organisms including staphylococci and a wide range of Gram negative organisms. Strains of Pseudomonas aeruginosa are resistant to neomycin, as are fungi and viruses.

5.2 Pharmacokinetic properties

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 may increase percutaneous absorption of topical corticosteroids.

Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids.

Once absorbed through the skin, the pharmacokinetics of topical corticosteroids are 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 kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

Studies performed with CLOTRIMAZOLE, BETAMETHASONE DIPROPIONATE & NEOMYCIN SULPHATE CREAM indicate that this topical combination antifungal/corticosteroid may have vasoconstrictor potencies in a range that is comparable to high potency topical corticosteroids. Therefore, use is not recommended in patients less than 17 years of age, in diaper dermatitis, and under occlusion. Neomycin is either not absorbed or is absorbed only minimally through intact skin. Any neomycin which is absorbed will be rapidly excreted by the kidneys in an unchanged state.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol
Cetostearyl Alcohol
Polyethylene Glycol 4000 (PEG 4000)
Cetomacrogol 1000
Glycerine
Liquid Paraffin
Disodium E.D.T.A
Disodium Hydrogen Phosphate
Stearic Acid
Butylated Hydroxy Toluene (B.H.T)
Chlorocresol (Para Chloro Meta Cresol)
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Month

6.4 Special precautions for storage

Store below 300C. Protect from light

6.5 Nature and contents of container <and special equipment for use, administration or implantation

30 gm Lami tube.

6.6 Special precautions for disposal <and other handling>

Keep out of reach of Children.

7. APPLICANT/MANUFACTURER

KENBARTH PHARMA LTD.
No 30 Sutools street,
Awada, Onistsha
Nigeria

8. DRUG PRODUCT MANUFACTURER

CIRON DRUGS & PHARMACEUTICALS PVT. LTD.
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