1. Name of medicinal product

ZAPIT CREAM (Betamethasone Dipropionate, Gentamicin Sulphate, Tolnaftate & Iodochlorhydroxyquinoline Cream)

2. Composition:

Each Gram contains:
Betamethasone Dipropionate USP……0.643 mg
Gentamicin Sulphate BP
Equivalent to Gentamicin base ……1.000mg
Tolnaftate USP……..10.000mg
Iodochlorhydroxyquinoline……10.000mg
Chlorocresol BP (As preservative)……1.000mg
Cream base .... q.s.

3. Pharmaceutical Form:

Topical Semi solid

4. Clinical Particulars

4.1 Indication

ZAPIT CREAM is indicated for the treatment of the various forms of eczema in children and adults including atopic and discoid eczemas; primary irritant and allergic dermatitis; psoriasis (excluding widespread plaque psoriasis); neurodermatoses including lichen simplex; intertrigo; discoid lupus erythematosus.

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

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, pityriasis versicolor, erythrasma and intertrigo.
iii. Skin diseases showing secondary infection with these fungi.
iv. Candidal nappy rash, vulvitis and balanitis.

4.2 Posology and Administration

Route of Administration: Topical

<u>Dosage and Administration</u>

ZAPIT CREAM should be applied thinly over the whole of the affected area and gently rubbed in. Initially, application should be made twice daily, but when improvement is seen, the intervals between applications may be extended and treatment eventually stopped. If

no improvement is seen within two to four weeks, reassessment of the diagnosis, or referral may be necessary. After cessation of treatment, should the condition recur, twice daily treatment should be re-instituted. However, when improvement is seen again, the intervals between applications may be gradually extended until maintenance dosing of application every third or fourth day is achieved. This is likely to avoid subsequent reappearance of the condition. The beneficial effects may be enhanced by preliminary use of hot soaks, or by intermittent applications or occlusive dressings.

Posology

There is no separate dosage schedule for the young or elderly.

Method of administration

The cream should be applied thinly and evenly to the affected area 2 – 3 times daily and rubbed in gently. A strip of cream (½ cm long) is enough to treat an area of about the size of the hand.

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 Contraindication

The cream should not be applied to the eyes. Rosacea, acne vulgaris; perioral dermatitis. Primary cutaneous viral infections (e.g. herpex simplex, chickenpox). Hypersensitivity to the preparation. Varicose ulcers or any other stasis ulcers. Use of ZAPIT CREAM Cream is not indicated in the treatment of primarily infected skin lesions caused by infection with fungi (e.g. candidiasis, tinea) or bacteria (e.g. impetigo); primary or secondary infections due to yeasts; perianal and genital pruritus; dermatoses in children under 1 year of age, including dermatitis and napkin eruptions.

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 Warning & precautions for use

Long-term continuous therapy should be avoided where possible, particularly in infants and children, as adrenal suppression can occur even without occlusion.

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 used in childhood, or on the face, courses should be limited if possible to five days and occlusion should not be used.

Topical corticosteroids may be hazardous in psoriasis for a number of reasons including rebound relapses, development of tolerance, risk of generalised pustular 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.

Appropriate antimicrobial therapy should be used whenever treating inflammatory lesions which have become infected.

Any spread of infection requires withdrawal of topical corticosteroid therapy and systemic administration of antimicrobial agents.

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

Fire hazard in contact with dressings clothing and bedding

Instruct patients not to smoke or go near naked flames - risk of severe burns. Fabric (clothing, bedding, dressings etc) that has been in contact with this product burns more easily and is a serious fire hazard. Washing clothing and bedding may reduce product build-up but not totally remove it.

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

Before using gentamicin, tell your doctor or pharmacist if you are allergic to it; or to other aminoglycoside antibiotics (such as tobramycin, amikacin); or if you have any

other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history. Rarely, this medication may be absorbed into the blood if you are applying it to large areas of skin, especially if the areas are cracked, broken, or raw. Injured skin may absorb more of this product, and the chance of serious side effects may increase. Consult your doctor for more details.

Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).

During pregnancy, this medication should be used only when clearly needed. Discuss the risks and benefits with your doctor.

It is unknown if this medication passes into breast milk. However, this drug is unlikely to harm a nursing infant. Consult your doctor before breast-feeding.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. None stated.

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.

The effects of some drugs can change if you take other drugs or herbal products at the same time. This can increase your risk for serious side effects or may cause your medications not to work correctly. These drug interactions are possible, but do not always occur. Your doctor or pharmacist can often prevent or manage interactions by changing how you use your medications or by close monitoring.

To help your doctor and pharmacist give you the best care, be sure to tell your doctor and pharmacist about all the products you use (including prescription drugs,

nonprescription drugs, and herbal products) before starting treatment with this product. While using this product, do not start, stop, or change the dosage of any other medicines you are using without your doctor's approval.

Some products that may interact with this drug include: aminoglycoside antibiotics given by injection (such as amikacin, gentamicin, tobramycin).

This document does not contain all possible drug interactions. Keep a list of all the products you use. Share this list with your doctor and pharmacist to lessen your risk for serious medication problems.

4.6 Fertility, Pregnancy and lactation

There is inadequate evidence of safety in human pregnancy. Topical administration of corticosteroids to pregnant animals can cause abnormalities of fetal development including cleft palate and intrauterine growth retardation. There may therefore be a very small risk of such effects in the human fetus.

<u>Pregnancy:</u>

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.

Pregnancy Category: C

Lactation: excreted in breast milk; no adverse effect on nursing infant Pregnancy Categories

A: Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.

B: May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.

C: Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.

D: Use in LIFE-THREATENING emergencies when no safer drug available. Positive evidence of human fetal risk.

X: Do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.

NA: Information not available.

4.7 Effects on ability to drive and use machines

None stated.

ZAPIT CREAM has no or negligible influence on the ability to drive or use machines.

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 used of large amounts, or treatment of extensive areas, can result in sufficient systemic absorption to produce the features of

hypercorticism. The effect is more likely to occur in infants and children, and if occlusive dressings are used. In infants, the napkin may act as an occlusive dressing.

Should systemic corticosteroid effects arise from application of ZAPIT CREAM Cream, topical treatment should be discontinued. If adrenal function is impaired the patient will need to be protected from any harmful effects of stress with oral corticosteroid preparations until normal adrenal function is established.

There are reports of pigmentation changes and hypertrichosis with topical steroids. In rare instances, treatment of psoriasis with corticosteroids (or its withdrawal) is thought to have provoked the pustular form of the disease (see precautions).

ZAPIT CREAM is usually well tolerated, but if signs of hypersensitivity appear, application should stop 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.

Skin irritation, redness, and itching may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly.

Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.

Rarely, use of this medication for prolonged or repeated periods may result in other types of skin infections (such as fungal or other bacterial infections). Contact your doctor if you notice any unusual skin symptoms or if your condition does not improve.

A very serious allergic reaction to this drug is rare. However, seek immediate medical attention if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

This is not a complete list of possible side effects. If you notice other effects not listed above, contact your doctor or pharmacist.

4.9 Overdose

Should systemic corticosteroid effects arise from application of ZAPIT CREAM topical treatment should be discontinued. If adrenal function is impaired the patient will need to be protected from any harmful effects of stress with oral corticosteroid preparations until normal adrenal function is established.

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.

This medicine may be harmful if swallowed. If someone has overdosed and has serious symptoms such as passing out or trouble breathing,. Otherwise, call a poison control center right away.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Beclometasone dipropionate is an active corticosteroid with topical anti-inflammatory activity.

Pharmacotherapeutic group:

ATC code:

Tolnafatate: D01AE18

Beclomethasone Dipropionate BP: D07CC04

Gentamicin Sulphate BP: D06AX07

Iodochlorhydroxyquinoline: D08AH30

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.

Bactericidal; appears to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S and 50S ribosomal subunits

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 systemically 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 and Gentamicin 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.

Absorption: Systemic absorption reported in burn patients treated with topical gentamicin

5.3 Pre-clinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that in other sections of the SmPC.

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.

6.0 Pharmaceutical particulars

6.1 List of excipients

Cetostearyl Alcohol

Ceto Mecrogol 1000

White Soft paraffin

Liquid Paraffin

Di Phosphate hydrogen phosphate

Purified water

Propylene Glycol

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

36 months from the date of manufacture.

6.4 Special Precautions for Storage

Do not store above 30°C

6.5 Nature and contents of container

30g tube pack in a carton along with insert.

7.0 Marketing Holder

Marketed By:

EVERDESTINY PHARMACEUTICALS LTD

Lagos, Nigeria.

Manufacturer

YASH MEDICARE PRIVATE LIMITED.

Near Sabar Dairy, Talod Road, P.O. Hajipur,

Tal. Himatnagar, Gujrat,India.