Summary of Product Characteristics
Clotrimazole and
Anhydrous Beclometasone Dipropionate Cream

1. NAME OF THE MEDICINAL PRODUCT

Candid – B Cream (Clotrimazole and Anhydrous Beclometasone Dipropionate Cream)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clotrimazole USP 1% w/w
Anhydrous Beclometasone Dipropionate BP 0.025% w/w

For list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Clotrimazole and Beclometasone Dipropionate Cream are indicated for the symptomatic relief and treatment of superficial fungal infections like dermatophyte infections and candidiasis of skin when accompanied by eczematous/inflammatory symptoms. It can also be used for steroid-responsive inflammatory dermatoses, secondarily complicated by fungal infections.

4.2 Posology and Method of Administration

The affected area should be washed with soap and water and dried thoroughly. A thin layer of Clotrimazole and Beclometasone Dipropionate Cream should be applied to cover the affected completely. The frequency of application is two to three times daily. Do not use for more than 4 weeks. For some patients, adequate maintenance therapy may be achieved with less frequent application.

Adult

- Clotrimazole and Beclometasone Dipropionate Cream should not be used for longer than 2 weeks for the treatment of tinea cruris and tinea corporis and no longer than 4 weeks for tinea pedis.
- Products containing only tinea cruris and tinea corporis, gently massage cream into the skin of the affected and surrounding area twice daily, morning and evening, for 2 weeks.
- For the treatment of tinea pedis, gentle massage cream into the skin of the affected and surrounding area twice daily, morning and evening, for 4 weeks.
- Clotrimazole and Beclometasone Dipropionate Cream should not be used with occlusive dressings.
- Patients not showing a clinical response within 3 to 5 days should be re-evaluated.
- The duration of therapy varies with type of infection and extent of the disease; however, treatment of cutaneous candidiasis and most dermatophyte infections usually requires 3 to 4 weeks.

Pediatric Use

- Clotrimazole and Beclometasone Dipropionate Cream should not be used for longer than 2 weeks for the treatment of tinea cruris and tinea corporis and no longer than 4 weeks for tinea pedis.
- No more than 45 grams per week is recommended for the cream. In children 12 years and older, for the treatment of tinea cruris and tinea corporis, gently massage cream into the skin of the affected and surrounding area twice daily, morning and evening, for 2 weeks. If improvement is not seen after 1 week, reassess condition. The product should NOT be used longer than 2 weeks.
- In children 12 years and older, for the treatment of tinea pedis, , gently massage cream into the skin of the affected and surrounding area twice daily, morning and evening, for 4 weeks. If improvement is not seen after 2 week, reassess condition. The product should NOT be used longer than 4 weeks.
- No uniform guidelines are available with regards to the use of steroid combination formulations in children due to vast individual variability and clinical inconsistency. But although topical Beclomethasone has been safely used in some infants and young children, use of the same in children less than 5 to 6 years of age warrants extreme caution, a clear clinical indication that justifies the potential risk and **strict medical supervision** due to higher chances of percutaneous absorption and side-effects.
- Use in children under 12 years old is not recommended, because of higher risk of percutaneous absorption and side-effects.
- Clotrimazole and Beclometasone Dipropionate Cream should not be used with occlusive dressings.
- The usage must be strictly under medical supervision. Lesser doses and lesser duration of therapy must be preferred in children.

4.3 Contraindications

Clotrimazole and Beclometasone Dipropionate Cream is contraindicated in patients who are sensitive to clotrimazole, beclomethasone dipropionate, other imidazoles or corticosteroids or to any of the excipients listed in section 6.1

Topical corticosteroids are contraindicated in infected skin lesions if no anti-infective agent is used simultaneously; fungal and viral infections of the skin, including herpes simplex, vaccinia and varicella; fungi (e.g. candida, tinea) or bacteria (e.g. impetigo); pregnancy.

Topical corticosteroids are also contraindicated in tuberculous lesions of the skin.

Clotrimazole and Beclometasone Dipropionate Cream is contraindicated in rosacea, acne, perioral dermatitis, varicose ulcers.

4.4 Special Warnings and Precautions for Use

Clotrimazole and Beclometasone Dipropionate Cream should not be used in or near the eyes since this preparation is not formulated for ophthalmic use. Topical corticosteroid preparations should be used with caution near the eyes; application to the eyelids may cause glaucoma.

General:
Topical corticosteroids
Systemic absorption of topical corticosteroids has produced reversible hypothalamicpituitary- adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients

Systemic absorption of topical corticosteroid agents will be increased with the use of more potent corticosteroid agents, with prolonged usage or if extensive body surface areas are treated. Therefore, patients receiving large doses of potent topical corticosteroids, applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression. If HPA axis suppression occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute with a less potent corticosteroid agent.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticotherapy.

If irritation or hypersensitivity develops with the use of Clotrimazole and Beclomethasone dipropionate Cream, treatment should be discontinued and appropriate therapy instituted.

Suitable precautions should be taken in using topical corticosteroids in patients with stasis dermatitis and other skin diseases with impaired circulation.

Prolonged use of corticosteroid preparations may produce striae or atrophy of the skin or subcutaneous tissue. If this occurs, treatment should be discontinued.

Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Pediatric use:
Safety and effectiveness in children below the age of 12 have not been established
The use of cream in diaper dermatitis is not recommended.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid induced HPA axis suppression and Cushing's syndrome than mature patients because of greater absorption due to a larger skin surface area to body weight ratio.

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

Administration of topical dermatologics containing a corticosteroid to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

In infants the napkin may act as an occlusive dressing, and hence these preparations should not be used in the nappy area for flexural eruptions. Ideally they should not be used in

infants and young children at all. Regular review should be made of the necessity for continuing therapy.

When topical anti-inflammatory steroids are used under occlusive dressing, over extensive areas, it is possible that sufficient absorption may take place to give rise to systemic effects. Such effects have not been reported with Beclomethasone dipropionate Cream. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

If signs of hypersensitivity appear, application should stop immediately. The least potent corticosteroids should be used with particular caution in facial dermatoses, and only for short periods.

Corticosteroids should never be used in the presence of infection except in conjunction with effective chemotherapy. 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 the skin should be cleansed before a fresh dressing is applied.

Excipient
This product contains methylhydroxybenzoate, which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

No information is available on drug interactions with topical Clotrimazole /Beclometasone combination. As systemic absorption is minimal, drug interactions with concomitant systemic medications are unlikely.

For clotrimazole, 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

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
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.

Corticosteroids have been shown to be teratogenic in animals following dermal application. As these agents are absorbed percutaneously, teratogenicity following topical application cannot be excluded. Therefore Beclomethasone dipropionate cream should not be used during pregnancy.

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.

The use of Beclomethasone dipropionate cream is not recommended during breast feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. From the undesirable effects noted in section 4.8, it is unlikely that treatment will have any effect on the ability to drive and use machines.

4.8 Undesirable effects

Clotrimazole cream
As the listed undesirable effects are based on spontaneous reports, assigning accurate frequency of occurrence for each is not possible.
Immune system disorders: allergic reaction (syncope, hypotension, dyspnea, urticaria).
Skin and subcutaneous tissue disorders: blisters, discomfort/pain, oedema, erythema, irritation, peeling/exfoliation, pruritus, rash, stinging/burning.

Beclomethasone dipropionate cream
Local burning, irritation, itching, skin atrophy, striae, hypertrichosis and adrenal suppression have been observed following topical corticosteroid therapy. Posterior subcapsular cataracts have been reported following the systemic use of corticosteroids.
It should be used for short courses only, as prolonged and intensive treatment may cause local atrophic changes in the skin such as thinning, loss of elasticity, dilatation of the superficial blood vessels, telangiectasia and ecchymosis. These changes are particularly likely to occur on the face, where occlusive dressings are used or where skin folds are involved. Prolonged use, use of large amounts, treatment of extensive areas, or application to damaged skin, when Beclomethasone dipropionate cream is used and when the occlusive dressing technique is applied can result in sufficient systemic absorption to produce the features of hypercortisonism such as depression of the hypothalamic-pituitary-adrenal axis with consequent suppression of the adrenal gland. These effects are most likely to be severe in infants and children. Growth may be retarded and a Cushingoid state may be produced. Benign intracranial hypertension has been reported less frequently.
Treatment of psoriasis with Beclomethasone dipropionate cream or its withdrawal may provoke the pustular form of the disease.
A steroid rosacea-like facies may be produced. This must be borne in mind when treating such conditions as psoriasis, discold lupus erythematosus, and severe eczema with Beclomethasone dipropionate cream.
Application of topical corticosteroid preparations to the eyelids may cause glaucoma.

4.9 Overdose

No specific antidote is available and treatment should be symptomatic.

Clotrimazole

Overdosage by topical clotrimazole administration is highly improbable, since application of C_{14} labelled clotrimazole to intact or diseased skin under occlusive dressing for 6 hours did not yield measurable quantities (lower detection limit 0.001 µg/mL) of radioactive material in the sera of human subjects.

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.

Beclomethasone dipropionate

Excessive or prolonged use of Beclomethasone dipropionate may result in systemic absorption of steroid and complications of steroid therapy, especially growth retardation in children, suppression of pituitary adrenal function, increased susceptibility to infection, hyperglycaemia, Cushingoid state and benign intracranial hypertension. Discontinuation of therapy, when the typical signs of hypercorticisim appear.

Treatment

Cessation of treatment with appropriate symptomatic and supportive treatment is indicated. Treat electrolyte imbalance, if necessary. In cases of chronic toxicity, slow withdrawal of corticosteroids is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungals for topical use – imidazole and triazole derivatives as well as anti-inflammatory steroid

Mechanism of Action:

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

Beclomethasone dipropionate is a glucocorticoid which has potent anti-inflammatory, antipruritic and vasoconstrictive properties. In the vasoconstriction test on human skin, beclomethasone dipropionate is five thousand times as potent as hydrocortisone.

Information on clinical study

It has been shown in clinical trials that the optimal concentration of beclomethasone dipropionate cream is 0.025%.
In two hundred and sixty-seven patients, Clotrimazole and beclomethasone dipropionate cream and fluocinolone acetonide were used simultaneously in a double-blind fashion. There was no significant difference in the action of the two substances. No side-effects or toxic reactions were reported. One patient discontinued treatment due to the development of a pruritic eruption during medication with another formulation of Clotrimazole and beclomethasone dipropionate cream (previously marketed lotion).

5.2 Pharmacokinetic properties

Skin penetration and systemic absorption of clotrimazole and beclomethasone dipropionate following topical application of Clotrimazole and Beclomethasone dipropionate cream have not been studied. The pharmacokinetic profile of the individual ingredients is as follows:

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 µg/ml, suggesting that clotrimazole applied topically is unlikely to lead to measurable systemic effects or side effects.

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 µg/cm^3 in the stratum corneum, to 0.5 to 1 µg/cm^3 in the reticular dermis, and 0.1 µg/cm^3 in the subcutis. No measurable amount of radioactivity (<0.001 µg/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.

Beclomethasone dipropionate

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.

5.3 Preclinical safety data

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.

Beclomethasone dipropionate

The carcinogenicity of beclomethasone dipropionate was evaluated in rats which were exposed for a total of 95 weeks, 13 weeks at inhalation doses up to 0.4 mg/kg/day and the remaining 82 weeks at combined oral and inhalation doses up to 2.4 mg/kg/day. There was no evidence of treatment-related increases in the incidence of tumors in this study at the highest dose, which is approximately 37 and 72 times the maximum recommended daily inhalation dose in adults and children, respectively, on a mg/m2 basis.

Beclomethasone dipropionate did not induce gene mutation in bacterial cells or mammalian Chinese Hamster ovary (CHO) cells in vitro. No significant clastogenic effect was seen in cultured CHO cells in vitro or in the mouse micronucleus test in vivo.

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day (approximately 250 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day (approximately 25 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). No inhibition of the estrous cycle in dogs was seen following 12 months of exposure to beclomethasone dipropionate by the inhalation route at an estimated daily dose of 0.33 mg/kg (approximately 17 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients are Liquid Paraffin, White Soft Paraffin, Cetomacrogol Emulsifying Wax, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Butylated Hydroxytoluene, Propylene Glycol, Sodium Dihydrogen Phosphate Dihydrate, Dibasic Sodium Phosphate Anhydrous, Benzyl Alcohol, Purified water.

6.2 Incompatibilities

None

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

A printed carton containing a leaflet and a printed aluminium collapsible tube containing white semi solid cream.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Ltd, India

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

May 2017