PROPOSED PROFESSIONAL INFORMATION FOR

MAXADERM

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MAXADERM (10 mg / 1 mg, cream)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of MAXADERM cream contains 10 mg of isoconazole nitrate (imidazole nitrate) and 1 mg of diflucortolone valerate.

Contains preservatives:

Propyl hydroxybenzoate 0,04 % m/m

Methyl hydroxybenzoate 0,16 % m/m

For the full list of excipients, see section **6.1**.

3. PHARMACEUTICAL FORM

Cream.

Ice white coloured homogenous cream with no visible particles or separation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAXADERM is indicated for the treatment of fungal infections of the skin, inguinal and genital regions accompanied by inflammation or eczematous skin conditions.

4.2 Posology and method of administration

Posology

Apply to the affected area twice daily.

In infections of the interdigital spaces, it is often advisable to place a strip of gauze smeared with MAXADERM between the toes or fingers.

After regression of the inflammation or eczematous skin condition, discontinue use of MAXADERM and follow up with the isoconazole preparation without corticoid additive. This applies in particular for use in inguinal and genital regions.

If a secondary microbial skin infection is present, suitable concomitant anti-microbial therapy should be instituted. If fungal infections are present, a topically active antimycotic should be applied.

Paediatric population

No data are available.

Method of administration

Cutaneous use.

4.3 Contraindications

MAXADERM is contraindicated in:

- patients with known hypersensitivity to isoconazole nitrate or diflucortolone valerate, or to any of the excipients in MAXADERM (see section **6.1**),
- the treatment of herpes simplex, vaccinia or varicella and tuberculosis of the skin,

- MAXADERM should not be used during pregnancy. 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,
- safety during lactation has not been established,
- potent topical corticosteroid preparations (MAXADERM) should not be applied to any skin crease areas,
- MAXADERM should not be applied with an occlusive dressing to large areas of the body,
- MAXADERM should not be used for the treatment of rosacea and should not be used indiscriminately for pruritis.

4.4 Special warnings and precautions for use

- If unfavourable reactions occur, treatment should be discontinued.
- If secondary microbial skin infection is present, suitable concomitant anti-microbial therapy should be instituted.
- MAXADERM should be used with particular caution in facial dermatoses, and only for short periods.
- MAXADERM should be used with caution near the eyes. Application to the eyelids has caused raised intraocular pressure, corneal ulcers, and reduced visual function.
- The treatment of psoriasis with MAXADERM may provoke the pustular form of the disease. Regular review should be made of the necessity for continuing therapy.
- MAXADERM should not be applied to ulcers of the leg and long term topical use is best avoided, especially in children.

Propyl hydroxybenzoate and methyl hydroxybenzoate

MAXADERM contains propyl hydroxybenzoate and methyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

Glaucoma may also develop from using local corticosteroids as in MAXADERM (e.g. after large-dosed or extensive application over prolonged period, occlusive dressing techniques, or application to the skin around the eyes).

In infections of the interdigital spaces, it is advisable to place a strip of gauze smeared with MAXADERM between the toes or fingers.

To avoid renewed infection, personal linen (facecloths, towels, underwear etc. preferably of cloth) should be changed daily and boiled.

Regular hygienic measures are essential for successful MAXADERM treatment. In tinea pedum, the space between the toes must be thoroughly dried after washing, and stockings or socks should be changed daily.

Cetostearyl alcohol may cause local skin reactions (e.g, contact dermatitis).

Potent topical corticosteroids should be used for short courses only. Regular review should be made of the necessity for continuing therapy.

Long term continuous or inappropriate use of topical steroids can result in the development of rebound flares after stopping treatment (topical steroid withdrawal syndrome). A severe form of rebound flare can develop which takes the form of a dermatitis with intense redness,

stinging and burning that can spread beyond the initial treatment area. It is more likely to occur when delicate skin sites such as the face and flexures are treated. Should there be a reoccurrence of the condition within days to weeks after successful treatment, a withdrawal reaction should be suspected. Re-application should be with caution and specialist advice is recommended in these cases or other treatment options should be considered.

4.5 Interaction with other medicines and other forms of interaction

None so far known.

Paediatric population

No information available.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

There are no adequate data from the use of diflucortolone valerate/isoconazole nitrate in pregnant women.

Use of topical preparations containing glucocorticoids is not recommended during the first trimester of pregnancy. In particular, treating large areas, prolonged use or occlusive dressings should be avoided during pregnancy.

Animal experimental studies with glucocorticosteroids have shown reproductive toxicity. The potential risk for humans is unknown.

A number of epidemiological studies suggest that there is an increased risk of oral clefts among newborns of women who were treated with systemic glucocorticosteroids during the first trimester of pregnancy. Oral clefts are a rare disorder and if systemic glucocorticosteroids are teratogenic, these may account for an increase of one or two cases per 1000 women treated while pregnant. Data concerning topical glucocorticosteroid use during pregnancy are insufficient, however, a lower risk might be expected since systemic availability of topically applied glucocorticosteroids is very low.

Adverse reactions cannot be excluded in neonates whose mothers have been treated during pregnancy (see section **4.8**).

Studies in animals (mice, rats and rabbits) have shown reproductive toxicity for diflucortolone valerate (see section **5.3**).

MAXADERM should not be used during pregnancy (see section **4.3**).

Breastfeeding

Safety in lactation has not been established.

It is not known whether isoconazole nitrate/diflucortolone valerate are excreted in human milk. A risk to the breast-fed infant cannot be excluded.

Nursing mothers should not be treated with MAXADERM on the breasts to avoid inadvertent ingestion by the child.

Use of MAXADERM is not recommended while breastfeeding, particularly for the treatment of large areas, prolonged use or occlusive dressings.

Adverse reactions cannot be excluded in children whose mothers have been treated while breast-feeding (see section **4.8**).

Fertility

Preclinical data did not indicate any risk on fertility.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed in patients treated with MAXADERM.

4.8 Undesirable effects

MedDRA system organ class	**Frequency**	**Side effects**
Eye disorders	*Frequency unknown*	Vision blurred.
Skin and subcutaneous tissue disorders	*Less frequent*	Striae.
	Frequency unknown (Cannot be estimated from available data)	Withdrawal reactions - redness of the skin which may extend to areas beyond the initial affected area, burning or stinging sensation, itch, skin peeling, oozing pustules. (see section **4.4**)
General disorders and administration site conditions	*Frequent*	Application site: irritation, burning.

	Less Frequent	Application site: erythema, dryness.
	Frequency unknown	Application site: pruritis, blisters.

Description of selected adverse reactions

Hypersensitivity reactions have occurred. Isoconazole may cause local reactions including burning and itching.

Long term continuous treatment with topical corticosteroids should be avoided as far as possible as this may cause atrophic changes in the skin leading to thinning, loss of elasticity, dilatation of superficial blood vessels, telangiectasiae and ecchymoses.

Increased fragility of cutaneous vessels may result in bruising and purpura. These changes are particularly likely to occur on the face and when occlusive dressings are used.

Systemic absorption of topically applied MAXADERM may occur, particularly under the following conditions: when large quantities are used, when application is made to wide areas of the body, or to damaged skin and when occlusive dressing technique is applied.

Depression of the hypothalamic-pituitary-adrenal axis with consequent suppression of the adrenal gland may occur and may be precipitated by an infection or trauma.

These effects are most likely to be severe in children. Growth retardation has been reported and a Cushingoid state may be produced.

Benign intracranial hypertension has been reported.

The following side effects may occur in rare cases: folliculitis, hypertrichosis, perioral dermatitis, skin discoloration, allergic skin reactions to any of the ingredients of the formulation.

Paediatric population

Side effects cannot be excluded in neonates whose mothers have been treated extensively or for a prolonged period of time during pregnancy or while lactating (for example, reduced adrenocortical function, when applied during the last weeks of pregnancy).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

See "Undesirable effects and Special warnings and Precautions for use".

Results from acute toxicity studies do not indicate that any risk of acute intoxication is to be expected following a single dermal application of an overdose (application over a large area under conditions favourable to absorption) or inadvertent oral ingestion.

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 13.4.1 Corticosteroids with or without anti-infective agents.

Pharmacotherapeutic group: imidazole and triazole derivatives, combinations.

ATC code: D01AC20.

Isoconazole nitrate is an antifungal agent with a broad spectrum of antifungal activity. It is effective against dermatophytes, yeasts, yeast-like fungi, moulds and is useful against the causative organisms of tinea versicolor and erythrasma.

Diflucortolone valerate has anti-inflammatory and anti-allergic properties. Diflucortolone valerate is a potent corticosteroid.

5.2 Pharmacokinetic properties

- Isoconazole nitrate

Isoconazole penetrates rapidly into human skin and reaches maximum concentration in the stratum corneum and underlying layers of the epidermis already 1 hour after application. High concentrations are maintained in the stratum corneum 6 hours after the last topical administration. Removal of the stratum corneum prior to application increases isoconazole concentration in the underlying epidermis.

Drug concentrations in the stratum corneum and epidermis exceeded minimum inhibitory and biocidal antimycotic concentrations (MIC) of most important pathogens (gram-positive bacteria and fungi) several-fold.

The concentration ratio between antimycotic and corticosteroid in the skin is increased in a ratio of 10:1 in comparison with that of the preparation indicating that antimycotic efficacy is not impaired by the corticosteroid.

Isoconazole is not metabolically inactivated in the skin. Systemic load due to percutaneous absorption is low. Even after removal of the horny layer, less than 1 % of the applied dose has reached the systemic circulation within 4 hours exposure time.

Isoconazole is completely metabolized and rapidly eliminated.

2,4-Dichloromandelic acid and 2-(2,6-dichlorobenzyloxy)-2-(2,4-dichlorophenyl)-acetic acid were characterized as quantitatively most important metabolites. A third of the labelled substances were excreted with the urine and two thirds in the bile. 75 % of the total dose was already excreted within 24 hours.

Isoconazole nitrate can be detected above the MIC in the stratum corneum and the hair follicles at one week after termination of a two-week application period.

- Diflucortolone valerate

Isoconazole does not influence penetration and percutaneous absorption of diflucortolone valerate. Diflucortolone valerate penetrates rapidly into the skin leading to horny layer levels of approximately 150 µg/mL (= 300 µmol/L) after one hour. Those levels are maintained for at least seven hours. Corticosteroid levels in the deeper epidermis were about 0,15 µg/mL (= 0,3 µmol/L).

Diflucortolone valerate is partly hydrolyzed in the skin to the likewise effective diflucortolone. The portion of the corticosteroid, which is percutaneously absorbed, is low. Within four hours exposure time, less than 1 % of the topically applied diflucortolone valerate dose is absorbed.

Entering the systemic circulation, diflucortolone valerate is rapidly hydrolyzed to diflucortolone and the corresponding fatty acid within minutes. Besides diflucortolone 11-keto-diflucortolone and two further metabolites have been detected in the plasma. Diflucortolone and all metabolites are eliminated from the plasma with half-lives of 4 to 5 hours for diflucortolone and approximately 9 hours for its metabolites and are excreted in a ratio of 75:25 with urine and faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cetomacrogol 1200

Cetostearyl alcohol

Citric acid monohydrate

Liquid paraffin

Macrogol cetostearyl ether

Methyl hydroxybenzoate

Polyoxyl 35 castor oil

Propylene glycol

Purified water

Propyl hydroxybenzoate

Sodium citrate dehydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25°C.

For external use only.

6.5 Nature and contents of container

20 g aluminium collapsible tube with a white polyester coating and a white polypropylene cap.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Rosen Heights,

Pasita Street,

Rosen Park,

Bellville,

7530,

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

33/13.4.1/0303

Namibia: NS2 11/13.4.1/0177

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation: 30 October 2000.

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

02 February 2024