SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRAVOCORT, 10 mg / 1 mg, cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g TRAVOCORT contains isoconazole nitrate 10 mg and diflucortolone valerate 1 mg in an easy-to-remove low fat base oil water emulsion.
Excipients with known effect: cetostearyl alcohol

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream.
White to slightly yellowish opaque cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fungal infections of hairless and hairy skin, e.g. in the region of the hands, the interdigital spaces of the feet, and in the inguinal and genital regions.

Because of the addition of diflucortolone valerate, TRAVOCORT is indicated for the initial or intermediate treatment of those fungal diseases which are accompanied by highly inflammatory or eczematous skin conditions.

4.2 Posology and method of administration

Posology

TRAVOCORT should be applied twice daily to the diseased areas of skin. In infections of the interdigital spaces it is often advisable to place a strip of gauze smeared with TRAVOCORT between the toes or fingers.

The treatment with TRAVOCORT must be terminated after regression of the inflammatory or eczematous skin condition and the therapy continued or followed up with the isoconazole nitrate 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

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Tuberculous or syphilitic processes in the area to be treated; virus diseases (e.g. varicella, herpes zoster), rosacea, perioral dermatitis and postvaccination skin reactions in the area to be treated.

- Potent topical corticosteroid preparations (TRAVOCORT) should not be applied to any skin crease areas.

- 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, TRAVOCORT should not be used during pregnancy.

4.4 Special warnings and precautions for use

Additional, specific therapy is required for bacterially infected skin diseases.

TRAVOCORT should not be allowed to come into contact with the eyes when being applied to the face.

Extensive application of topical corticosteroids such as TRAVOCORT to large areas of the body or for prolonged periods of time, in particular under occlusion, significantly increases the risk of side effects.

These effects are more likely to occur in children.

Glaucoma may also develop from using local corticoids as in TRAVOCORT (e.g. after large-dosed or extensive application over a 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

TRAVOCORT between the toes or fingers.

To avoid renewed infection, personal linen (face-cloths, towels, underwear etc. - preferably of cotton) should be changed daily and boiled.

Regular hygienic measures are essential for successful TRAVOCORT 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. Reapplication should be with caution and specialist advise is recommended in these cases or other treatment options should be considered.

4.5 Interactions 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).

TRAVOCORT 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 TRAVOCORT on the breasts to avoid inadvertent ingestion by the child.
Use of TRAVOCORT 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 TRAVOCORT.

4.8 Undesirable effects

a. Summary of the safety profile

Local symptoms such as itching, burning, erythema or vesiculation may occur in isolated cases under treatment with TRAVOCORT.

In clinical studies, most frequently observed adverse reactions included application site irritation and application site burning.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Eye disorders	Frequency not known	Vision blurred*.
Skin and subcutaneous tissue disorders	Less frequent	Striae.
	Frequency not known (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*.
General disorders and administration site conditions	Frequent	Application site: irritation, burning.
	Less frequent	Application site: erythema, dryness.
	Frequency not known	Application site: pruritis, blisters.

*See also section 4.4.

c. Description of selected adverse reactions

The following reactions may occur when topical preparations containing corticoids such as TRAVOCORT are applied to large areas of the body (about 10 % and more) or for long periods of time (more than 4 weeks) or under occlusion:

Local symptoms such as atrophy of the skin, telangiectasia, striae, acneiform changes of the skin.

Systemic effects may include depression of the hypothalamic-pituitary-adrenal axis with consequent suppression of the adrenal gland possibly leading to growth retardation or a cushiongoid state. Benign intracranial hypertension may occur.

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.

d. 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 13.4.1 Corticosteroids without anti-infective agents.
Pharmacotherapeutic group and ATC code: imidazole and triazole derivatives, combinations, D01AC20

Isoconazole nitrate is for use in the treatment of superficial fungal diseases of the skin. It is effective against dermatophytes and yeasts, yeast-like fungi and moulds, and the causative microorganisms of pityriasis versicolor, as well as against the causative organism of tinea versicolor and that of erythrasma.

Serial dilution testing demonstrated the unchanged spectrum of action of isoconazole nitrate against dermatophytes, yeasts, yeast-like fungi, moulds, and gram-positive bacteria even after the addition of diflucortolone valerate in a 10:1 ratio combination. Furthermore, the addition of isoconazole nitrate did not affect the anti-inflammatory and vasoconstrictive properties of diflucortolone valerate (rat ear test and Wells experimental design).

Diflucortolone valerate is a potent fluorinated corticosteroid with vasoconstrictive properties and suppresses inflammation in inflammatory and allergic skin conditions and alleviates the subjective

complaints such as pruritis, burning and pain. It reverses capillary dilatation, intercellular oedema and tissue infiltration whilst capillary proliferation is suppressed.

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.

The percutaneously absorbed portion was too low to investigate the fate of isoconazole nitrate within the human organism. Therefore 0.5 mg of ^{3}H-labelled isoconazole nitrate was intravenously injected. 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.

5.3 Preclinical safety data

After topical application to rabbits higher levels of the antimycotic were obtained in the skin as compared to the corticosteroid-free preparation. This was interpreted as a retardation of percutaneous absorption as consequence of the vasoconstrictive effect of the corticosteroid.
Studies in animals (mice, rats and rabbits) have shown reproductive toxicity for diflucortolone valerate.
In specific reproduction toxicity studies, isoconazole nitrate exerted no restrictive effect on any phase of the reproductive cycle.
In vitro and *in vivo* investigations for detection of gene-, chromosome- and genome mutations have not given any indications of a mutagenic potential of diflucortolone valerate or isoconazole nitrate.
Specific tumorigenicity studies have neither been carried out with diflucortolone valerate nor isoconazole nitrate.
Results from mucosal tolerance investigations on the rabbit eye show an irritative effect on the conjunctiva following inadvertent contact of the eyes with TRAVOCORT.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cetostearyl alcohol
Disodium edetate
Paraffin, liquid
Paraffin, white soft
Polysorbate 60
Sorbitan stearate
Water purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Store at or below 25 °C.

5 years.

After first opening: 3 months

6.4 Special precautions for storage

Not applicable.

6.5 Nature and contents of container

Tubes of 15 or 20 g made of aluminium with a high-density polyethylene HD-PE white screw cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand, 1685

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

South Africa: N/13.4.1/171

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 November 1981

10. DATE OF REVISION OF THE TEXT

09 May 2023

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