Bayer HealthCare

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

TRAVOCORT CREAM
Broad-spectrum antimycotic with a corticoid additive

COMPOSITION:

1 g TRAVOCORT contains isoconazole nitrate (1-[2,4-dichloro-β-(2,6-dichlorobenzyloxy)-phenethyl]-imidazole, nitrate) 10 mg and diflucortolone valerate (6α,9-difluoro-11β-hydroxy-21-valeryloxy-16α-methyl-1,4-pregna-diene-3,20-dione) 1 mg in an easy-to-remove low fat base oil water emulsion.

PHARMACOLOGICAL CLASSIFICATION:

A 13.4.1 Corticosteroids with anti-infective agents.

PHARMACOLOGICAL ACTION:

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, as well as against the causative organism of tinea versicolor and that of erythrasma.

Diflucortolone valerate is a potent fluorinated corticosteroid with vasoconstrictive properties and suppresses inflammation in inflammatory and allergic skin conditions. It reverses capillary dilatation, intercellular oedema and tissue infiltration whilst capillary proliferation is suppressed.

Pharmacodynamic properties:

Isoconazole nitrate is for use in the treatment of superficial fungal diseases of the skin. It displays a very broad spectrum of antimicrobial action. It is effective against dermatophytes and yeasts, yeast-like fungi (including the causative organism of pityriasis versicolor) and moulds, as well as against the causative organism of erythrasma.

Diflucortolone valerate suppresses inflammation in inflammatory and allergic skin conditions and alleviates the subjective complaints such as itching, burning and pain.

Pharmacokinetic properties:

- Isoconazole nitrate

Isoconazole penetrates rapidly into human skin and reaches maximum levels in the horny layer and in the living skin already 1 hour after application. 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.

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.

- 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.

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.

CONTRA-INDICATIONS:

Hypersensitivity to the active substances or to any of the excipients.
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.

WARNINGS:

Additional, specific therapy is required in 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.

INTERACTIONS:

None so far known.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.
There are no adequate data from the use of diflucortolone valerate in pregnant women.
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.

TRAVOCORT should not be used during pregnancy and lactation.
Nursing mothers should not be treated with TRAVOCORT on the breasts.

DOSAGE AND DIRECTIONS FOR USE:

Unless otherwise instructed, 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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

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

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, acneform 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.
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).

Special precautions:

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

White to slightly yellowish cream.

PRESENTATION:

Tubes of 15 or 20 g made of aluminium with screw cap.

STORAGE INSTRUCTIONS:

Store below 25 °C. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

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Namibia: 90/13.4.1/025
Botswana: B9312310

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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