ARTWORK

LEO Pharma A/S
Internal Market Access

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Subject: INS 148 x 210 mm		Date: 08/02/22	Date
Colour: Black		Sign.: EBD	Sign.

Preparation Strength Packsize	Place of production
Travocort® Cream	Italy

Segrate no:	Replaces Segrate no:	Comments:
000000	063371	Page 1 of 2 Font size: 8 pt Mock-up for reg. purpose

IIT004-00 - Page 1 + 2 - 148 x 210 mm – DRA_90040

Travocort® Cream

Broad-spectrum antimycotic with a corticoid additive

Manufactured By: LEO Pharma Manufacturing Italy S.r.l.
Important information, please read carefully!

1. NAME OF THE MEDICINAL PRODUCT

Travocort 1 %/0.1 % cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g Travocort contains 10 mg (1 %) isoconazole nitrate and 1 mg (0.1 %) diflucortolone valerate.

3. PHARMACEUTICAL FORM

Travocort contains a white to slightly yellowish opaque cream. 1 g Travocort cream contains 10 mg isoconazole nitrate and 1 mg diflucortolone valerate in an easy-to-remove low fat base (o/w emulsion).

4. CLINICAL PARTICULARS

4.1 Indication
Initial or interim treatment of those superficial fungal infections of the skin which are accompanied by highly inflammatory or eczematous skin conditions, e.g. in the region of the hands, the interdigital spaces of the feet, and the inguinal and genital regions.

4.2 Dosage and method of administration
Travocort should be applied twice daily to the diseased areas of skin. The treatment with Travocort must be terminated after regression of the inflammatory or eczematous skin condition, at the latest, however, after 2 weeks, and the therapy continued or followed up with the corticoid-free preparation Travogen. This applies in particular for use in the inguinal and genital regions.

4.3 Contraindications
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.

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

4.4 Special warnings and precautions for use
Specific additional therapy is required for bacterial infections of the skin.

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

Extensive application of topical glucocorticoids to large areas of the body or for prolonged periods of time, in particular under occlusion, may increase the risk of systemic side effects.

As known from systemic glucocorticoids, glaucoma may also develop from using local glucocorticoids (e.g. after large-dosed or extensive application over a prolonged period, occlusive dressing techniques, or application to the skin around the eyes).

The physician should advise the patients on hygienic measures during the treatment.
If Travocort is applied to the genital regions, the excipients liquid paraffin and soft paraffin may cause damage of latex products for barrier methods such as condoms and diaphragms used concomitantly, thus impairing their effectiveness.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.

4.6 Pregnancy and lactation
Pregnancy
There are no data from the use of isoconazole nitrate/ diflucortolon-21-valerate in pregnant women.
Studies in animals (mice, rats and rabbits) have shown reproductive toxicity for diflucortolone-21-valerate.
In general, the use of topical preparations containing glucocorticoids should be avoided during the first trimester of pregnancy. In particular, treating large areas, prolonged use or occlusive dressings should be avoided during pregnancy.
Epidemiological studies suggest that there could possibly be an increased risk of oral clefts among newborns of women who were treated with glucocorticoids during the first trimester of pregnancy.
The clinical indication for treatment with Travocort must be carefully reviewed and the benefits weighed against the risks in pregnant women.

Lactation
It is unknown whether isoconazole nitrate/diflucortolone-21-valerate are excreted in human milk. A risk to the suckling child cannot be excluded.
Nursing mothers should not be treated on the breasts.
Treating large areas, prolonged use or occlusive dressings should be avoided during lactation.
The clinical indication for treatment with Travocort must be carefully reviewed and the benefits weighed against the risks in lactating women.

4.8 Undesirable effects
Summary of the safety profile
In clinical studies, most frequently observed adverse reactions included application site irritation and application site burning.

Tabulated list of adverse reactions
Frequencies of adverse reactions observed in clinical studies and given in the table below are defined according to the MedDRA frequency convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

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1. PROOF FROM EBD	Mock-up Approval Stamp (MAS)		
Date 08/02/22	**Graphic Design**	**Editorial Proof**	**Second Approver**
New proof requested ☐	**According to:** SOP_000647, SOP_000962, SOP_003993 and SOP_008676 ☐	**According to:** SOP_000647, SOP_000962 and SOP_008676 ☐	Product name ☐
Sign.:	1st Sign.: Date:	Sign.: Date:	Dosage form ☐
Date:	2nd Sign.: Date:		Strength/Stripes ☐
			Pack size ☐
			Prompts ☐
			Material No./Reg. No. ☐
			Barcode ☐
			Sign.: Date:

System Organ Class	Common	Uncommon	Frequency not known
General disorders and administration site conditions	Application site: - irritation, - burning	Application site: - erythema, - dryness	Application site: - pruritus - vesicles
Skin and sub-cutaneous tissue disorders		Skin striae	

Description of selected adverse reactions
As with other glucocorticoids for topical application, the following local adverse reactions may occur (frequency not known): Skin atrophy, application site folliculitis, hypertrichosis, telangiectasia, perioral dermatitis, skin discoloration, acne, and/or allergic skin reactions to any of the ingredients of the formulation. Systemic effects due to absorption may occur when topical preparations containing glucocorticoids are applied.
Adverse reactions 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, immunosuppression).

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 favorable to absorption) or inadvertent oral ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 molds, as well as against gram-positive bacteria *in-vitro* and against the causative organism of erythrasma.

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

5.2 Pharmacokinetic properties
Isoconazole nitrate
Isoconazole penetrates rapidly into human skin from Travocort cream and reaches maximum drug concentrations in the horny layer and in the living skin already 1 hour after application.

After topical application to rabbits higher levels antimycotic concentrations were obtained in the skin as compared to the corticosteroid-free preparation. This was interpreted as a retardation of percutaneous absorption of isoconazole nitrate as consequence of the vasoconstricitive effect of the corticosteroid.

Furthermore, the concentration ratio between antimycotic and corticosteroid in the skin is increased as compared to a ratio of 10:1 present in the Travocort cream, 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 percutaneous absorbed portion was too low to investigate the fate of isoconazole nitrate within the human organism. Therefore 0.5 mg of ^{3}H-labeled isoconazole nitrate was injected intravenously. Isoconazole is completely metabolized and rapidly eliminated.

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

Diflucortolone valerate
Isoconazole dose 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 hour exposure time, less than 1% of the topically applied Travocort dose have been percutaneously absorbed.

Entering the systemic circulation, diflucortolone valerate is 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 respectively all metabolites are eliminated from the plasma with half-lives of 4-5 hours and approx. 9 hours respectively (half-lives after i.v. injection) and are excreted in a ratio of 75:25 with urine and feces.

6. PHARMACEUTICAL PARTICULARS

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

Incompatibilities
Not applicable

Storage
Store below 30°C.
Store all drugs properly and keep them out of reach of children.

Shelf Life
Refer to Carton.

Dosage form and packaging available
Tubes of 10 g.

Name and address of manufacturing holder
LEO Pharma Manufacturing Italy S.r.l.
Via E. Schering, 21
20054 Segrate (Ml)
Italy.

Date of revision of the text
01 Nov 2019

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