SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product
Travocort 0.1 + 1% w/w Cream

2. Qualitative and Quantitative Composition
Contains 0.1% w/w diflucortolone valerate (1 mg/g) and 1% w/w isoconazole nitrate (10 mg/g).

Excipient with known effect: cetostearyl alcohol

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form
Cream.
A white to yellowish opaque cream.

4. Clinical Particulars

4.1 Therapeutic indications
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 in the inguinal and genital regions.

4.2. Posology and method of administration

Cutaneous use

Travocort should be applied twice daily to the diseased areas of skin.

Treatment with Travocort must be terminated after regression of the inflammatory or eczematous skin conditions or at the latest after 2 weeks and therapy continued or followed up with a glucocorticoid-free anti-fungal preparation. This applies in particular for use in the inguinal and genital regions.

Paediatric population:

Dose adjustments are not required when Travocort is administered to children aged 2 years or older and adolescents.

Only limited data on the safety of Travocort in children aged below 2 years are available, for more details see section 5.1.

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.

In general, Travocort should be used without occlusion.

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.

This medicinal product contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Studies in animals (mice, rats and rabbits) have shown reproductive toxicity for diflucortolone valerate. Travocort should be avoided during the first trimester of pregnancy. In particular, treating large areas, prolonged use or occlusive dressings should be avoided during the whole of 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.

Breast-feeding

It is unknown whether isoconazole nitrate/diflucortolone 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.

Fertility
Preclinical data did not indicate any risk on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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).

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	

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 discolouration, 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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Malta

ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal.

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

Pharmacotherapeutic group: Imidazole and triazole derivatives, combinations
ATC Code: D01AC20

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 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 aspruritus, burning and pain.

Experience of Travocort in the paediatric population are given in the table below. One hundred and ninety-five paediatric subjects aged < 18 years were included in 6 clinical studies (4 randomized, double-blind multicentre comparative and 2 non-controlled open-label studies). The age distribution and efficacy results are provided.

Infants (1-23 months) n (%)	**Children** (2 ≤ - <12 years) n (%)	**Adolescents** (12≤ - <18 years) n (%)	**Total** n (%)	**Age (years)*** mean	median	
20 (10.3)	41 (21.0)	134 (68.7)	195 (100) (90 females / 102 males / 3 missing)	11.9	14	
Efficacy**						
11 (55.0)	25 (60.9)	88 (67.2)	124 (63.6)			Very good (cleared)
4 (20.0)	13 (31.7)	35 (26.7)	52 (26.7)			Good
2 (10.0)	1 (2.5)	5 (3.8)	8 (4.1)			Moderate
3 (15.0)	2 (4.9)	3 (2.3)	8 (4.1)			Poor

*Age definitions according to ICH E11 **Efficacy ratings from three patients were missing

5.2 Pharmacokinetic properties
Isoconazole nitrate:
Isoconazole penetrates rapidly into human skin from Travocort cream and maximum drug concentrations in the horny layer and in the living skin are present 1 hour after application. High concentrations were maintained for at least 7 hours (horny layer: approx. 3500 µg/ml (corresponding to 7 mmol/l), living epidermis approx. 20 µg/ml (40 µmol/l), dermis approx. 3 µg/ml (6 µmol/l). Removal of the horny layer prior to the application increased isoconazole concentrations in the living

skin approximately by a factor of 2. Drug concentrations in the horny layer and the epidermis exceeded minimum inhibitory and biocidal antimycotic concentrations (MIC) of most important pathogens (dermatophytes, molds and yeasts) several-fold and reached MIC values in the dermis.

In a further study, isoconazole nitrate could still be detected above the MIC in the stratum corneum and the hair follicles at one week after termination of a two-week application period. In some subjects, isoconazole nitrate could even be detected 14 days after the last application.

After topical application to rabbits of the 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 a consequence of the vasoconstrictive 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 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-labelled isoconazole nitrate was injected intravenously. Isoconazole is completely metabolised and rapidly eliminated.

2,4-Dichloromandelic acid and 2-(2,6-dichlorobenzyloxy)-2-(2,4-dichlorophenyl)-acetic acid were characterised as quantitatively most important metabolites. A third of the labelled 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 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 hydrolysed 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 Travocort dose has been percutaneously absorbed.

Entering the systemic circulation, diflucortolone valerate is hydrolysed 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 – 5 hours and approximately 9 hours respectively (half-lives after i.v. injection) and are excreted in a ratio of 75:25 with urine and faeces.

5.3 Preclinical safety data
In systemic tolerance studies following repeated dermal and subcutaneous administration, the effect of diflucortolone valerate was that of a typical glucocorticoid. Following repeated dermal application of

the active substance combination only those effects typical of glucocorticoids were observed. It can be derived from these results that no side effects other than these which are typical of glucocorticoids are to be expected following therapeutic use of Travocort under extreme conditions such as application over large areas and/or occlusion. There were no indications of possible interaction with isoconazole nitrate. The results from repeated dose systemic tolerance studies on isoconazole nitrate do not suggest that systemic effects of the antimycotic have to be expected under therapy with Travocort.

Embryotoxicity studies with Travocort led to results typical for glucocorticoids, i.e. embryolethal and/or teratogenic effects are induced in the appropriate test system. In view of these findings, particular care should be taken when prescribing Travocort during pregnancy. The results of epidemiological studies are summarized under section "*4.6 Fertility, pregnancy and lactation*".

In a series of special reproduction toxicity studies, isoconazole exerted no adverse effects on any phase of the reproductive cycle. In particular, the active ingredient showed no teratogenic potential. Although no controlled clinical studies have been carried out, experience in the use of preparations containing isoconazole nitrate during pregnancy does not indicate any risk of embryotoxic effects.

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 with isoconazole nitrate. On the basis of the pharmacodynamic action pattern, the lack of evidence of a genotoxic potential, the structural properties and the results of chronic toxicity tests (no indication of proliferative changes), there is no suspicion of a tumorigenic potential of either of the active substances. Since systemically effective immunosuppressive dosages will not be reached after dermal application of Travocort if used as directed, no influence on the occurrence of tumours is to be expected.

According to the results from local tolerance studies following repeated dermal administration of diflucortolone valerate alone and in combination with isoconazole nitrate, no dermal changes further to the side-effects already known for topical preparations containing glucocorticoids are to be expected from therapy with Travocort.

Results from mucosal tolerance investigations on the rabbit eye show that a slight irritative effect is to be expected on the conjunctiva following inadvertent contamination of the eyes with Travocort.

6. Pharmaceutical Particulars

6.1. List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30 °C.

6.5 Nature and contents of container
Tubes with 15 g made of pure aluminium, interior wall coated with epoxy resin, and with a polyester-based external coating, fold seal ring is made of polyamide based heat sealable material. The screw cap is made of high density polyethylene.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
No special requirements

7. Marketing Authorisation Holder
LEO Pharma A/S
Industriparken 55
2750 Ballerup
Denmark

8. Marketing Authorisation Number(s)

9. Date of First Authorisation/Renewal of the Authorisation
Date of First Authorisation: 23rd January 2008
Date of Renewal: 17th January 2014

10. Date of Revision of the Text
November 2019