SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
TRACOVOL 1% + 0.1% Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Active substances:
1 gram of TRACOVOL contains 10 mg (1%) isoconazole nitrate and 1 mg (0.1%) diflucortolone valerate as active ingredients.

Excipients:
Cetostearyl alcohol ..... 60 mg
Disodium EDTA ..... 15 mg
For excipients, see section 6.1

3. PHARMACEUTICAL FORM
Cream
Homogeneous, white colored cream

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
TRACOVOL is suitable for the initial and intermediate treatment of superficial fungal infections of the skin (e.g., on the hands, between the toes, in the groin, and in the genital area) accompanied by severe inflammatory or eczematous reactions.

4.2 Posology and method of administration
Posology/frequency and duration of administration
TRACOVOL is applied twice daily. Following the disappearance of inflammatory or eczematous symptoms, or no later than 2 weeks after the start of treatment, TRACOVOL is discontinued and treatment is continued with a non-glucocorticoid-containing antifungal preparation. This applies particularly to the groin and genital areas.

Method of administration
It is applied topically to the affected skin area.

Additional information on special populations
Renal/Hepatic impairment
Systemic absorption following the use of high-potency topical corticosteroids over a long period of time, on large surface areas, under occlusion, or in patients with concomitant hepatic impairment may result in reversible hypothalamic-pituitary-adrenal (HPA) axis suppression.

Pediatric population
No dose adjustments are necessary when TRACOVOL is administered to children aged 2 years or older and adolescents.

There is only limited data available on the safety of the combination of isoconazole nitrate and diflucortolone valerate in children younger than 2 years of age.

It should be used with caution in children due to the risk of increased systemic absorption and side effects.

4.3 Contraindications

It is contraindicated in cases of tuberculosis or syphilis in the treatment area; in viral infections (e.g., varicella, herpes zoster), rosacea, perioral dermatitis, and post-vaccination skin reactions in the treatment area.

It is contraindicated in patients with hypersensitivity to any of the ingredients in the formulation.

4.4 Special warnings and precautions for use

When used in bacterial skin infections, specific additional treatment is required.

Long-term or intensive application of topical glucocorticoids, especially under occlusive dressings, may increase the risk of systemic side effects.
Caution should be exercised when applying to the face, groin area, or armpits, and when used in children, due to the increased risk of side effects. In addition, the increase in systemic absorption in children should be taken into account.

When applying to the face, care should be taken to avoid getting TRACOVOL in the eyes.

As with systemic glucocorticoids, the use of topical glucocorticoids (e.g., high doses over a long period, application to a large area, occlusive dressings, or application to the skin around the eyes) may lead to glaucoma.
Cross-resistance has been observed between isoconazole and miconazole, econazole, and tioconazole.
If TRACOVOL is applied to the genital area, the excipients liquid paraffin and soft paraffin may cause damage that reduces the effectiveness of latex products used in contraceptive methods such as condoms and diaphragms.

TRACOVOL contains cetostearyl alcohol. Cetostearyl alcohol may cause skin reactions (e.g., contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction

There are no known interactions.

Additional information for specific populations
There is no available data for special populations.

Pediatric population
No data is available for the pediatric population.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is C.

Women of child-bearing potential / Contraception
There is insufficient data on the use of isoconazole nitrate and diflucortolone valerate in pregnant women.

Glucocorticoids have been shown to cause reproductive toxicity in animal studies (see Section 5.3). Preclinical data have not shown any risk to fertility.
If TRACOVOL is applied to the genital area, the excipients liquid paraffin and soft paraffin may cause damage that reduces the effectiveness of latex products used in preventive methods such as condoms and diaphragms.

Pregnancy
There are no data on the use of isoconazole nitrate and diflucortolone valerate in pregnant women. Studies in animals (mice, rats, and rabbits) have shown reproductive toxicity for diflucortolone valerate (see Section 5.3). In general, topical preparations containing glucocorticoids should be avoided during the first three months of pregnancy. In particular, prolonged use or occlusive dressings should be avoided on large treatment areas during pregnancy.

Epidemiological studies of the combination of isoconazole nitrate and diflucortolone valerate suggest that women treated with glucocorticoids during the first trimester of pregnancy may have an increased risk of oral cleft in their newborn infants.

The clinical indication for treatment with TRACOVOL should be carefully reviewed, and the risks and benefits should be evaluated in pregnant women.

Lactation
It is unknown whether isoconazole nitrate and diflucortolone valerate are excreted in breast milk.

The risk to breastfed infants cannot be ignored.
The clinical indication for treatment with TRACOVOL should be carefully reviewed in lactating women, and the benefits and risks should be carefully weighed.

It should not be applied to the breasts of breastfeeding women. During breastfeeding, large treatment areas, prolonged use, or occlusive dressings should be avoided.

Reproduction ability / Fertility
Preclinical data have shown no risk to fertility.

4.7 Effects on ability to drive and use machines
There are no data to indicate that TRACOVOL affects the ability to drive or use machines.

4.8 Undesirable effects
In clinical studies, the most commonly observed adverse reactions at the application site were irritation and burning at the application site.
The frequency of side effects observed in clinical studies is listed below according to the MedDRA classification: 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), not known (cannot be estimated from the available data).

Skin and subcutaneous tissue disorders:
Uncommon: Stria

General disorders and conditions related to the application area

Common: Irritation and burning at the application site
Uncommon: Erythema and dryness in the application area
Unknown: Itching and vesicles in the application area

As with other topical glucocorticoids, the following adverse reactions may occur (frequency unknown): Skin atrophy, application site folliculitis, hypertrichosis, telangiectasia, perioral dermatitis, skin discoloration, acne, and/or allergic skin reactions to any of the ingredients in the formulation. When preparations containing glucocorticoids are applied, systemic effects related to absorption may occur.

When TRACOVOL is applied for a long time or over large areas in women during pregnancy or lactation, some adverse reactions may also occur in newborns (e.g., decreased adrenal gland function, immunosuppression).

Additional information for specific populations:
Renal/Hepatic insufficiency:
Systemic absorption following the use of high-potency topical glucocorticoids for prolonged periods, over large surface areas, under occlusion, or in patients with concomitant hepatic impairment may result in reversible hypothalamic-pituitary-adrenal (HPA) axis suppression.

Pediatric population:
No dose adjustments are necessary when TRACOVOL is administered to children aged 2 years or older and adolescents.

There is only limited data available on the safety of the combination of isoconazole nitrate and diflucortolone valerate in children younger than 2 years of age.

It should be used with caution in children due to the risk of increased systemic absorption and side effects.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 in accordance with local requirements.

4.9 Overdose
Based on the results of acute toxicity studies, no risk is expected following a single excessive dose applied to the skin (application to a large area under conditions conducive to absorption) or accidental oral ingestion.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Imidazole and Triazole derivatives
ATC code: D01AC20

Isoconazole nitrate is used for the treatment of superficial fungal infections of the skin. It has a broad

spectrum of antimicrobial activity. It is effective against dermatophytes, yeasts and yeast-like fungi (including organisms causing *Pityriasis* versicolor), molds, as well as *in vitro* gram-positive bacteria and organisms causing Erythrasma.

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

5.2 Pharmacokinetic properties

Isoconazole nitrate:

Absorption:
Isoconazole nitrate rapidly penetrates the skin, and maximum active ingredient concentration is reached in living skin and the stratum corneum 1 hour after application.

Isoconazole nitrate is not metabolically activated in the skin. Systemic exposure as a result of percutaneous absorption is very low. Even after 4 hours of application following removal of the horny layer, less than 1% of the applied dose has entered the systemic circulation.

Biotransformation:
The most important metabolites in terms of quantity are 2,4-dichloromandelic acid and 2-(2,6-dichlorobenzyloxy)-2-(2,4-dichlorophenyl)-acetic acid. Isoconazole is not inactivated by metabolism in the skin.

Elimination:
In terms of monitoring the fate of isoconazole nitrate in the body, the amount absorbed percutaneously is insufficient. For this reason, 0.5 mg $^{(3)\ of}$H-labeled isoconazole nitrate was injected intravenously, and it was observed that isoconazole was completely metabolized and rapidly eliminated. One-third of the labeled substance is excreted in the urine, and two-thirds in the bile. Seventy-five percent of the total dose is excreted within 24 hours.

Linearity/non-linearity:
No data are available regarding linearity/nonlinearity.

Diflucortolone valerate:

Absorption:
Isoconazole does not affect the penetration and percutaneous absorption of diflucortolone valerate. The amount of corticosteroid absorbed percutaneously is low. Less than 1% of the combination of topically applied isoconazole nitrate and diflucortolone valerate was absorbed percutaneously during a 4-hour application.

Distribution:
Diflucortolone valerate rapidly penetrates the skin, reaching levels of approximately 150 µg/ml (=300 µmol/l) in the stratum corneum within one hour. These active ingredient levels persist for at least 7 hours. Corticosteroid levels in the deep epidermal layer are approximately 0.15 µg/ml (=0.3 µmol/l).

Biotransformation:
Diflucortolone valerate is partially hydrolyzed in the skin and converted to diflucortolone, which has the same activity. Diflucortolone valerate that enters the systemic circulation is hydrolyzed within

minutes to diflucortolone and the corresponding fatty acid. In addition to diflucortolone, 11-keto-diflucortolone and two other metabolites have been identified in plasma.

Elimination:
Diflucortolone is eliminated from plasma with a half-life of 4-5 hours, while its metabolites have a half-life of approximately 9 hours (half-lives after IV injection), with 75% excreted in urine and 25% in feces.

Linearity/non-linearity:
No data are currently available regarding linearity/nonlinearity.

Pharmacokinetic/pharmacodynamic relationship(s)
After topical application of the isoconazole nitrate/diflucortolone valerate combination to rabbits, higher antifungal levels were obtained in the skin compared to preparations without corticosteroids. This was considered to be due to delayed percutaneous absorption as a result of the vasoconstrictive effect of the corticosteroid.

Antifungal and corticosteroid concentrations in the skin were observed at a higher ratio than the 10/1 ratio present in the isoconazole nitrate/diflucortolone valerate combination, indicating that the antifungal efficacy is not impaired by the corticosteroid.

5.3 Preclinical safety data

Systemic tolerance studies following repeated dermal and subcutaneous applications show that the effect of diflucortolone valerate is the same as that of typical glucocorticoids. Following repeated dermal application of the active ingredient combination, only typical glucocorticoid effects were observed. Based on these results, no side effects other than typical glucocorticoid side effects are expected following therapeutic use of the isoconazole nitrate/diflucortolone valerate combination, even under extreme conditions such as application to large areas and/or occlusive therapy. There is no potential interaction with isoconazole nitrate.

Based on the results obtained from repeated dose systemic tolerance studies, no systemic antimycotic effect is expected during treatment with the isoconazole nitrate/diflucortolone valerate combination.

Embryotoxicity studies conducted with the combination of isoconazole nitrate and diflucortolone valerate yielded results typical for glucocorticoids, i.e., the appropriate test system showed embryolethal and/or teratogenic effects.

In light of these findings, special caution is required when prescribing TRACOVOL during pregnancy.

The results of epidemiological studies are summarized in the section titled "4.6 Pregnancy and lactation."

In specific studies conducted to evaluate reproductive toxicity, isoconazole nitrate did not cause any adverse effects in any phase of the reproductive cycle. In particular, the active substance did not show any teratogenic potential. Although no controlled clinical studies have been conducted, experience with the use of preparations containing isoconazole nitrate during pregnancy has shown no risk of embryotoxic effects.

In vitro and *in vivo* experiments investigating gene, chromosome, and genome mutations have not revealed any evidence of mutagenic potential for diflucortolone valerate and isoconazole nitrate.

No specific tumorigenicity studies have been conducted with diflucortolone valerate and isoconazole nitrate.
Considering the pharmacodynamic effect model, the absence of evidence of genotoxic potential, their structural properties, and the results of chronic toxicity tests (no evidence of proliferative changes), there is no evidence that either active substance has tumorigenic potential.

Since systemic effective doses are not reached with the dermal application of the isoconazole nitrate/diflucortolone valerate combination, it is not expected to have an effect on tumor formation.

Based on the results of local tolerance studies conducted with repeated dermal applications of diflucortolone valerate alone and in combination with isoconazole nitrate, no changes in the skin are expected during treatment with the isoconazole nitrate/diflucortolone valerate combination, apart from the known side effects of glucocorticoids.

Results from mucosal tolerance studies conducted in rabbits indicate that accidental contamination of the eye with the isoconazole nitrate and diflucortolone valerate combination may cause mild conjunctival irritation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate (Tween) 60
Sorbitan monostearate
Cetostearyl alcohol
Paraffin liquid
Disodium EDTA
Paraffin, white soft
Deionised water

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 30ºC.

6.5 Nature and contents of container

In a box, sealed with a white HDPE cap with a twist-off lid, aluminum tube, 15g.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed according to local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER
2017/154

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 27.03.2017
Date of last renewal :

10. REVISION DATE OF TEXT