SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Travocort 1% + 0.1% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: Each g of Travocort cream contains 50mg cetostearyl alcohol.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Cream
White to yellowish, opaque cream.

4. CLINICAL INFORMATION

4.1 Therapeutic indications

Initiation of treatment or intermediate treatment of superficial fungal skin infections of the skin accompanied by highly inflammatory or eczematous skin conditions, e.g. in the areas of the interdigital spaces of the feet, hands, inguinal and genital regions.

4.2 Posology and method of administration

Dosage

Travocort cream is applied twice daily to the affected area of the skin.

Duration of treatment
Treatment with Travocort cream should be stopped after resolution of inflammatory or eczematous skin conditions, at the latest after two weeks of treatment, and treatment may be continued with a glucocorticoid-free antifungal preparation if necessary. This is mainly recommended for the inguinal and genital regions.

Paediatric population

No dose adjustment is required when Travocort is used in children aged 2 years or older and adolescents.

Only limited data on the safety of Travocort in children below 2 years of age are available.

Travocort cream is recommended to be used in the paediatric population only if imperative with particular caution and under immediate medical supervision.

Method of administration

Cutaneous use.

4.3 Contraindications

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

Travocort cream should not be used if tuberculous or syphilitic lesions, viruses (e.g. chickenpox, herpes simplex, herpes zoster), rosacea, common acne, perioral dermatitis, primary suppurative skin infections, atrophic or thin skin, dull ulcers, sores and skin reactions after vaccination are present at the application site.

Also, topical corticosteroid preparations should not be used in burns, because they interfere with healing.

Travocort cream should not come into contact with mucous membranes, including the mucous membrane of the eyes.

4.4 Special warnings and precautions for use

In bacterial infections of the skin, special additional treatment is required.

The possibility of infection with resistant organisms must also be taken into account. In this case, it is recommended to stop using the product and apply the appropriate treatment.

In general, Travocort should be used without dressing. When a watertight dressing is applied, a recommendation should be made to clean the skin to avoid possible contamination.

Application of topical glucocorticoids to large areas of the body or for a prolonged period of time, particularly by dressing, can significantly increase the risk of systemic side effects. In general, long-term treatment with topical corticosteroids should be avoided to avoid changes in the skin.

Do not use Travocort cream (due to topical corticosteroid) for more than two weeks without review by a dermatologist.

When applying to the face, care should be taken so that Travocort cream does not come into contact with the eyes.

Visual disturbances

Visual disturbances may be reported with both systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, then referral to an ophthalmologist should be considered to evaluate possible causes that may include cataracts, glaucoma or rare diseases such as central serous chorioretinopathy (COHA) that have been reported following the use of systemic and topical corticosteroids.

As is known from systemic glucocorticoids, glaucoma may also develop from the use of topical glucocorticoids (e.g. when used in large doses or with extended application for a prolonged period of time, or by dressing or applying to the skin around the eyes). If topical use is made on the face, care should be taken so that the drug does not come into contact with the eye.

Particular care should be taken when applying the drug to the face, since the skin on the face is particularly sensitive, and local side effects are more likely. Long-term treatment with topical corticosteroids should not be carried out on the face to avoid skin changes.

After repeated application, at least 10-15 days, a temporary decrease or loss of corticosteroid activity (especially fluorinated) may occur due to rapid storage. This phenomenon is restored after stopping use for a few days or weeks.

In psoriasis, topical corticosteroids should be administered sparingly and with specialist supervision, because in addition to the temporary benefit, in the long term and after stopping treatment, there is a risk of worsening the disease.

Due to adverse reactions from possible absorption, it should not be applied to large areas of skin (more than 10% of body surface) and/or occlusive dressing (bandages, etc.), or prolonged administration, particularly in children (see below "Paediatric population"), pregnant women (see below "4.6 Fertility, pregnancy and lactation"), patients with severe kidney disease, bleeding diathesis and forthcoming vaccinations.

Symptoms may recur after stopping treatment. Corticosteroid preparations may change the clinical picture of some skin diseases and make it difficult to make a clear diagnosis.

In general, the least potent corticosteroid considered effective for the intended indication should be chosen and another of the same strength or greater strength should be administered in case of non-response.

The physician should advise patients on hygiene measures during treatment.

If Travocort cream is applied to the genital area, liquid paraffin and soft paraffin excipients can damage latex contraceptive products, such as condoms and diaphragms, when used simultaneously with the cream, thereby reducing their effectiveness.

Travocort cream contains ketostearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis).

Paediatric population

Avoid long-term use in children. Due to adverse reactions from possible absorption, caution should be exercised when applied to large areas of skin, and/or with occlusive dressing (bandages, etc.), or prolonged administration, especially in children. Children are more prone to systemic side effects from topical corticosteroid use because they may absorb larger amounts of medication due to a larger skin area relative to body weight.

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 on the use of isoconazole nitrate/diflucortolone valerate in pregnant women.

Experience with the use of proprietary medicinal products containing isoconazole nitrate during pregnancy has shown no teratogenic risk in humans.

Local application of potent corticosteroids in pregnant animals has caused abnormalities in fetal development.

Studies in animals (mice, rats and rabbits) have shown reproductive toxicity of diflucortolone valerate (see section 5.3). In general, the use of topical preparations containing glucocorticoids should be avoided during the first trimester of pregnancy. In particular, treatment on large skin surfaces, prolonged use or tight dressing should be avoided throughout pregnancy.

Epidemiological studies suggest that there may be an increased risk of oral cleft in newborns whose mothers were treated with glucocorticoids in the first trimester of pregnancy.

The use of Travocort cream during pregnancy should be carefully evaluated and the benefits to the mother weighed against the risks to the foetus, and if imperative should be used with caution and under immediate medical supervision.
At the end of pregnancy, the foetus may be at risk of adrenal cortex atrophy (see section 4.8), which requires gradual substitution therapy in newborns.

Breastfeeding

It is unknown whether isoconazole nitrate/ diflucortolone valerate is excreted in human milk. The risk to the breastfed child cannot be excluded.

Other glucocorticoids are excreted in breast milk. Travocort cream should therefore not be used during breastfeeding. The use of Travocort cream during breastfeeding should be carefully evaluated. If corticosteroid use during breastfeeding is considered

necessary, breastfeeding should be discontinued. Avoid contact of the baby with the areas of skin where Travocort cream is applied.

Fertility
Preclinical data show no risk to fertility.

4.7 Effects on ability to drive and use machines

Travocort cream has no influence on the ability to drive and use machines.

However, if visual disturbances occur, patients should not drive and/or use machines and should contact their doctor.

4.8 Side effects

Summary of the safety profile

In clinical studies, the most commonly observed side effects include irritation and burning at the application site.

Tabulated summary of adverse reactions

The frequencies of adverse reactions observed in clinical studies 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
Eye disorders			Vision, blurred (see also section 4.4)
General disorders and administration site conditions	Application site: -irritation -burning	Point of application: erythema -aridity	Application site: -itching -Pustules
Disorders of the skin and subcutaneous tissue		Striae of the skin	

Description of selected adverse reactions

As with other glucocorticoids for topical application, the following local adverse reactions may occur (frequency not known): skin atrophy, folliculitis at the site of application, hirsutism, telangiectasias, perioral dermatitis, skin discoloration, acne and

/ or allergic skin reactions to any of the components of the preparation. Systemic effects due to absorption may occur when topical preparations containing glucocorticoids are applied.

Paediatric population

Adverse reactions cannot be excluded in neonates whose mothers have received treatment on extensive areas of the skin or for a prolonged period of time during pregnancy or while breastfeeding (for example, decreased function of the adrenal cortex, immunosuppression).

Local effects after long-term topical use

The adverse effects that have been reported with potent topical corticosteroids at their application sites are:

Burning sensation, itching, irritation, dryness, folliculitis, hypopigmentation, thinning of the skin, telangiectasias.

Modification of the clinical picture on incorrect use in fungal infections or scabies. Secondary infection, local microbial infections (onset of latent infection or progressive worsening), fungal infections, facilitating the onset of molluscum contagiosum (infectious tinea) and condylomas acuminata (genital warts).

Inhibition of wound healing, acne elements, pustules, summer sweat, perioral dermatitis, rash in the form of rosacea, recurrence of pustular psoriasis upon discontinuation of treatment (Rebound Phenomenon), skin atrophy in the form of scar, linear striae, spider veins, porphyria, diffuse erythema, papular-vesicular atypical rashes, allergic hypersensitivity, local hirsutism, skin discoloration. If symptoms of hypersensitivity occur, administration should be stopped immediately.

The above side effects are not common, but may occur more frequently with the use of a watertight dressing or after long-term topical use.

General after long-term topical use

Suppression of the function of the cortico-adrenal axis, a drop in the level of cortisol in plasma – Cushing's syndrome.

Reporting suspected adverse reactions

It is important to report suspected adverse reactions following marketing authorisation of the medicinal product. It allows continuous monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions through ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

Side effects can also be reported to the responsible entity.

4.9 Overdose

No risk of acute toxicity is expected from single dermal application, overdose (application over a large surface under conditions conducive to absorption) or accidental oral ingestion.

Prolonged and excessive use can lead to skin irritations and skin atrophy, as well as a sedative effect on the adrenal cortex due to increased absorption. Skin irritation and

action on the adrenal cortex are reversible upon discontinuation of treatment, but cutaneous atrophy may remain.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungals for dermatological use - Imidazole and triazole derivatives - Imidazoles/triazoles in combination with corticosteroids

ATC Code: D01AC20

Isoconazole nitrate is a broad-spectrum antifungal and is indicated for the treatment of superficial cutaneous mycoses. It is effective against dermatophytes, blastomycetes, blastomycete-like fungi (including the causative agent of pityriasis variegated) and moulds, as well as against gram-positive bacteria *in vitro* and against the causative agent of erythrasma.

Diflucortolone valerate belongs to the class of powerful glucocorticosteroids and suppresses inflammation in inflammatory and allergic skin conditions and relieves underlying discomforts such as itching, burning and pain.

After topical application, Travocort cream suppresses manifestations of the inflammatory reaction such as edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, collagen deposition, fibroblast proliferation and scar formation. Steroids inhibit inflammatory action against mechanical, chemical or immunological agents.

The mechanism of anti-inflammatory action is thought to work by intensifying the vasoconstrictive effect of adrenaline, stabilising the lysosome membrane, slowing down macrophage motility, inhibiting quinine release, inhibiting lymphocyte and neutrophil function as well as prostaglandin synthesis and, on prolonged use, reducing antibody production.

Paediatric population

The experience of Travocort in the paediatric population is given in the table below. 195 paediatric patients less than 18 years of age were included in 6 clinical studies (4 randomised, double-blind multicentre comparators and 2 uncontrolled open label studies). The results of age distribution and efficacy shall be provided.

Infants (1-23 μηνών) n (%)	**Children** (2-12 years) n (%)	**Adolescents** (12-18 years) n (%)	**Total** n (%)	**Age (years)***	
				Average	Interstitial

20 (10,3)	41 (21,0)	134 (68,7)	195 (100) (90 Girls / 102 boys / 3 except**)	11,9	14
Effectiveness					
11 (55,0)	25 (60,9)	88 (67,2)	124 (63,6)	Very good	
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)	Low	

**Age definitions according to ICH E11*

*** Missing efficacy evaluations from three patients*

General characteristics of topical corticosteroids Penetration and local action

In order to act locally, corticosteroids must penetrate the skin. The extent of absorption and therefore the clinical effect, as well as most adverse reactions, depend, as has been shown, both on the substance itself and for a certain corticosteroid, and on several factors.

(a) Concentration of the medicinal product

A further increase in concentration after a certain concentration of the drug on a given inert basis does not result in proportionally greater potency, but on the contrary increases the occurrence of adverse reactions.

(b) Pharmaceutical form

The penetration of the active ingredient depends on the physicochemical properties of the base. The presence of other components or excipients may alter penetration through the stratum corneum and/or the effect (e.g. salicylic acid, urea, propylene glycol, antibiotics and antiseptics, tar).

(c) Spreading area

The limited penetration of the drug into areas such as the soles and palms is due to their thick stratum corneum. For the opposite reasons, rapid and significant absorption can be observed through, for example, the skin of the scrotum, the eyelids, and, to a somewhat lesser extent, the skin of the forehead and scalp.

(d) Skin condition

Penetration increases in injured or affected skin (eg, abrasions or pathological conditions, such as parakeratosis). However, the affected or injured stratum corneum is restored after a few days of treatment.

(e) Spreads conditions

The coating promotes penetration and can occur unintentionally when infant diapers are used or when intertributes or folds are coated.

Potency

The potency of a product is determined by its penetration into the skin, the endogenous activity of the drug and the rate of its removal. Among the known corticosteroids, it is customary to distinguish, depending on the substance and concentration, four levels of activity: mild, moderately strong, strong and very strong. The boundaries between categories, particularly between intermediate categories (moderately strong and strong) are difficult to define. Some corticosteroids are available in different concentrations, on the basis of which they can be classified in a different potency class. In addition, the effect of the inert agent on potency may result in transfer to an adjacent activity category.

The active substance of Travocort cream, Diflucortolone valerate 0.1%, according to the potency classification of topical corticosteroids belongs to the category *"Strong-II"*.

5.2 Pharmacokinetic properties

 Isoconazole nitrate

Isoconazole from Travocort cream quickly penetrates human skin and reaches maximum concentrations in the stratum corneum and skin an hour after application. High concentrations were maintained for at least 7 hours (stratum corneum: approx. 3,500 µg/ml (corresponding to 7 mmol/l), epidermis: approximately 20 µg/ml (40 µmol/l), skin: approximately 3 µg/ml (6 µmol/l). Removal of the stratum corneum prior to application increased isoconazole concentrations in the skin by approximately a factor of 2. Concentrations of the drug in the stratum corneum and epidermis exceeded minimum inhibitory (MIC) and biocidal products antifungal concentrations of the most important pathogens (dermatophytes, fungi and yeasts) multiple times and reached MIC values in the skin.

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

After topical application to rabbits, higher concentrations of the antifungal were found on the skin than in the cream that did not contain corticosteroids. This means that there is a delay in percutaneous absorption of isoconazole nitrate as a consequence of the vasoconstrictor effect of the corticosteroid.

In addition, the ratio of antifungal to corticosteroid concentration in the skin is increased compared to the 10:1 ratio present in Travocort cream. This means that the antifungal activity is not affected by the corticosteroid.

Isoconazole is not metabolically neutralized in the skin. The systematic burden on the body due to transdermal absorption is low. Even after removal of the stratum corneum,

less than 1% of the administered dose penetrated the general bloodstream after four hours of skin exposure to the substance.

The transdermal absorption of isoconazole nitrate is too low for metabolism to be investigated by the human body. Therefore, 0.5 mg of 3H-labelled isoconazole nitrate was administered by the intravenous route. Isoconazole is completely metabolized and rapidly excreted from the human body.

The most important metabolites were identified as 2,4dichloroamygdalic acid and 2(2,6-dichlorobenzyloxy)-2-(2,4-dichlorophenyl)acetic acid. One-third of radioactively labelled metabolites are excreted in urine and two-thirds in bile. 75% of the dose is excreted within the first 24 hours.

- Diflucortolone valerate

The degree of absorption of topical corticosteroids is determined by many factors, such as the concentration of the drug, its pharmaceutical form (excipients), the area of the spread (difficulty in absorption in a thick stratum corneum), the condition of the skin (increase of absorption into the skin with its continuity lysis) and the use of a watertight dressing (substantial increase in absorption).

After absorption through the skin, topical corticosteroids follow the pharmacokinetic course of systemic administration. They bind to varying degrees to plasma proteins. They are metabolized primarily in the liver and excreted through the kidneys. Some of the topical corticosteroids and their metabolites are also excreted in bile.

Isoconazole does not affect the penetration and transdermal absorption of Diflucortolone valerate. Diflucortolone valerate quickly penetrates the skin, reaching the stratum corneum, at values of approximately 150 µg/ml (= 300 µmol/l) after one hour. These values shall be maintained for at least 7 hours. Corticosteroid values in deeper layers of the epidermis were approximately 0.15 µg/ml (= 0.3 µmol/l).
Diflucortolone valerate is partially hydrolysed with the product of Diflucortolone of similar action. The percentage of corticosteroid absorbed transdermally is low. After 4 hours of exposure, less than 1% of the dose of topically applied Travocort cream was absorbed transdermally.

When it reaches the systemic circulation, Diflucortolone valerate is hydrolyzed within a few minutes to Diflucortolone and the corresponding fatty acid. In addition to Diflucortolone, 11-keto- Diflucortolone and two other metabolites were detected in plasma. Diflucortolone is excreted from plasma with a half-life of approximately 4-5 hours, and all metabolites with a half-life of approximately 9 hours (half-lives determined after intravenous administration) and excreted in urine and faeces at a rate of 75:25.

5.3 Preclinical safety data

In systemic tolerability studies, after repeated dermal and subcutaneous administration, Diflucortolone valerate exhibited a typical glucocorticoid activity. After repeated dermal administration of the combination of active substances, only the characteristic effects of glucocorticosteroids were observed. From these results it can be concluded that, after use of Travocort cream for therapeutic reasons and under extreme conditions

such as application to large areas of skin and tight dressing, no side effects other than those typical for glucocorticoids can be expected. No interactions with isoconazole nitrate were observed. Based on the results of systematic repeated dose tolerability studies with isoconazole nitrate, systemic effects of the antifungal are not expected during treatment with Travocort cream.

Embryotoxicity studies with Travocort cream resulted in results typical for glucocorticoids, i.e. embryomortality and/or teratogenicity, induced in the appropriate test systems. Considering these findings, special care should be taken when prescribing Travocort cream during pregnancy. The results of the epidemiological studies are summarised in section 4.6 "Fertility, pregnancy and lactation".

In a series of specific reproductive toxicology studies, isoconazole did not experience adverse reactions at any stage of the reproductive cycle. In particular, there was no evidence of teratogenicity. Although no controlled clinical studies have been conducted, no risk of embryotoxic effects is expected from the experience of using isoconazole nitrate-containing preparations during pregnancy.

In vitro *and* in vivo *experiments to detect mutations in genes, chromosomes and genome showed no mutagenic activity of isoconazole nitrate or Diflucortolone valerate.*

No specific tumoricity studies were conducted with either Diflucortolone valerate or isoconazole nitrate. Based on the pharmacodynamic scheme of action, the absence of evidence of genotoxicity, structural properties and the results of chronic toxicity tests (there was no evidence of change in reproduction), tumour is not suspected for either active substance. As long as systemically effective immunosuppressive dosages are not to be achieved following dermal administration of Travocort cream and if the preparation is used as instructed, no effect on tumour occurrence is expected.

According to results of local tolerability studies, after dermal administration of valerian Diflucortolone alone and in combination with isoconazole nitrate, no skin changes are expected from treatment with Travocort cream, except for known adverse reactions of topical medicinal products containing glucocorticoids.

Taking into account the results of tolerance tests observed in rabbit eyes, slight conjunctival irritation is to be expected, following accidental contact of Travocort cream with the eye.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 60, sorbitan
stearate, cetostearyl
alcohol, Liquid
paraffin,
White soft paraffin,
Disodium edetate dihydrate,
Purified water.

6.2 Incompatibilities Not

applicable.

6.3 Shelf life 5

years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

30g tube made of pure aluminum, the inner wall with epoxy-resin coating, as well as outer cover based on polyester. The folded sealing ring consists of a polyamide base that is heat sealed. The screw cap is made of high-density polyethylene.

6.6 Special precautions for disposal No

special obligation.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PARALLEL IMPORT LICENSE HOLDER

EJ Busuttil, Busuttil Buildings; Triq l-Ghadam, Central Business District Zone , Birkirkara CBD 1060

8. PARALLEL IMPORT LICENSE NUMBER

PI/1411/10601A

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

07th May 2025

10. DATE OF REVISION OF THE TEXT