

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OLY[®] Plus Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Contains 10 mg (1%) of isoconazole nitrate and 1 mg (0.1 %) of diflucortolone valerate.

Excipients:

Cetostearyl alcohol	50,00 mg
Disodium EDTA	1,00 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

OLY[®] Plus is suitable for initial or interim treatment of 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

Posology/frequency and duration of administration:

OLY[®] Plus is applied twice daily.

Treatment with OLY[®] Plus 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 preparation. This applies in particular for use in the inguinal and genital regions.

Method of administration:

It is applied externally to the diseased areas of the skin.

Additional Information on Special Populations:

Renal/Hepatic Failure:

The reversible hypothalamic pituitary adrenal (HPA) axis suppression occurs following systemic absorption associated with the prolonged use of high-potency topical corticosteroids on large surface areas, under occlusion, or in patients with concomitant hepatic insufficiency.

Pediatric population:

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

4.3 Contraindications

It is contraindicated in case of tuberculosis or syphilis; virus diseases (e.g. varicella, herpes zoster), rosacea, perioral dermatitis and post-vaccination skin reactions in the area to be treated. Hypersensitivity to the active substances or to any of the excipients.

In general, OLY[®] Plus should be used without occlusion.

4.4 Special warnings and precautions for use

Caution is required for bacterial infections of the skin; specific additional therapy may also be necessary.

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.

Caution should be exercised when being applied to the face, groin and armpits and used in children due to the increased risk of side effects. The increase in systemic absorption in children should also be considered.

OLY[®] Plus should not be allowed to come into contact with the eyes when being applied to the face.

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).

In the case of interdigital infection, it is recommended to place an OLY[®] Plus applied gauze between the fingers or toes.

To prevent recurrent infections, personal clothing (cotton products should be preferred as hand and face cloths, towels, underwear, etc.) should be changed and boiled every day.

Regular hygiene measures are essential for the success of treatment with OLY[®] Plus. In case of fungal infections of the feet, after the feet are washed, the fingers should be well dried and the socks should be changed every day.

Cross-resistance against miconazole, econazole and tioconazole is seen with isoconazole.

OLY[®] Plus contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).

OLY[®] Plus contains sodium. However, it does not require any warning because of the method of use.

4.5 Interaction with other medicinal products and other forms of interaction

There is no known interaction.

4.6 Fertility, pregnancy and lactation

General recommendation

Pregnancy category is C.

Women with childbearing potential / Contraception

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

Studies in animals have shown reproductive toxicity for glucocorticoids. (see part 5.3)

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 cleft palate is a rare genetic disease and if the systemic glucocorticoids are teratogenic, it means one or two more cases per 1000 women treated during pregnancy. Data on topical glucocorticoid use during pregnancy are inadequate. However, the systemic effects of topical glucocorticoids are very low, so a lower rate should be expected.

As a general rule, topical preparation containing should be avoided during the first trimester of pregnancy. The clinical indication of treatment with OLY[®] Plus should be carefully reviewed and the benefits weighed against the risks in pregnant women. In particular, treating large areas, prolonged use or occlusive dressings should be avoided during the whole of pregnancy.

Lactation

The clinical indication for treatment with OLY[®] Plus must be carefully reviewed and the benefits weighed against the risks in lactating women. Especially, treating large areas should be avoided. Nursing mothers should not be treated on the breasts.

Fertility

In a series of specific reproductive toxicity studies, isokonazole nitrate did not cause any side effects in any phase of the reproductive cycle.

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 OLY[®] Plus.

4.8 Undesirable effects

Application of topical preparations containing corticosteroids over a large area (10% or more of the body surface) or for a prolonged time (4 weeks or longer) may result in the following side effects: skin atrophy, telangiectasia, striae, acne-like changes and systemic effects due to corticosteroid resorption.

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

Immune system disorders:

Rare: Allergic contact dermatitis

Skin and subcutaneous disorders:

Rare: Local symptoms such as folliculitis, hypertrichosis, perioral dermatitis, discoloration, rash, itching, burning, erythema or vesiculation, irritation, dryness, maceration, rash.

These are mild and usually transient side effects resulting from the use of topical corticosteroids; complaints disappeared after the treatment. Following topical treatment, approximately 1% of patients may experience local effects such as itching or burning.

Local irritation and burning occurred in 0.5% to 4% of patients receiving topical treatment with diflucortolone valerate.

When OLY[®] Plus is administered over a prolonged or extended period during pregnancy or lactation, it is possible that some side effects may occur in newborns (eg reduction in adrenal function in the last weeks of pregnancy).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkish Pharmacovigilance Center (TUFAM) (www.titck.gov.tr e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

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: Antifungal (imidazole derivative) combined with Potent (Group III) corticosteroid for topical use

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.

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

5.2 Pharmacokinetic properties

General properties

- Isoconazole nitrate:

Absorption

Isoconazole penetrates rapidly into human skin and maximum drug concentrations in the horny layer and in the living skin are present 1 hour after application.

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.

Biotransformation

2,4-Dichloromandelic acid and 2-(2,6-dichlorobenzyloxy)-2-(2,4-dichlorophenyl)-acetic acid were characterized as quantitatively most important metabolites.

Isoconazole is not metabolically inactivated in the skin.

Elimination

The percutaneous absorbed portion was too low to investigate the fate of isoconazole nitrate within the human organism. Therefore 0.5 mg of ³H-labelled isoconazole nitrate was injected intravenously. Isoconazole is completely metabolized and rapidly eliminated.

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.

- Difflocortolone valerate:

Absorption

Isoconazole does not influence penetration and percutaneous absorption of difflocortolone valerate. The portion of the corticosteroid which is percutaneously absorbed is low. Within four hours exposure time, less than 1 % of the topically applied isoconazole nitrate / difflocortolone valerate has been percutaneously absorbed.

Distribution

Difflocortolone 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).

Biotransformation

Difflocortolone valerate is partly hydrolysed in the skin to the likewise effective difflocortolone. Entering the systemic circulation, difflocortolone valerate is hydrolysed to difflocortolone and the corresponding fatty acid within minutes. Besides difflocortolone, 11- keto – difflocortolone and two further metabolites have been detected in the plasma.

Elimination

Difflocortolone 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.

Pharmacokinetic/pharmacodynamics relations

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.

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 isoconazole nitrate / diflucortolone valerate 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 do not suggest that systemic effects of the antimycotic have to be expected under therapy with isoconazole nitrate / diflucortolone valerate.

Embryotoxicity studies with isoconazole nitrate / diflucortolone valerate 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 OLY® Plus 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 isoconazole nitrate / diflucortolone valerate 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 isoconazole nitrate / diflucortolone valerate.

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 isoconazole nitrate / diflucortolone valerate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Paraffin, liquid
Paraffin, white soft
Polysorbate 60
Cetostearyl alcohol
Disodium EDTA
Sorbitan stearate
Deionized water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of container

Aluminum tube with 15 g sealed with HDPE screw cap, placed in a box.

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

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

2015/135

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13.02.2015
Date of last renewal: 13.02.2015

10 DATE OF REVISION OF THE TEXT

13.02.2015