SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MANTAZOL Cream

2. QUALITIVE AND QUANTITIVE COMPOSITION

Active ingredient: 1 g MANTAZOL, 10 mg (1%) isoconazole nitrate and 1 mg (0,1 %) diflucortolone valerate

Excipient(s): Cetostearly alcohol 0.75 g
See 6.1 for excipient(s)

3. PHARMACEUTICAL FORM

Viscous homogeneous, opaque white cream

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MANTAZOL is suitable for the 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

Posology /the frequancy and duration of administration:
MANTAZOL should be applied twice daily.

Treatment with MANTAZOL must be terminated after regression of the inflammatory or eczematous skin conditions or at the latest after 2 weeks from starting thearpy and thearpy is followed up with corticosteroid-free cream. This applies in particular for use in the inguinal and genital regions.

Method of administration:
MANTAZOL is administered topically applying to the diseased areas of skin externally.

Additional information on special populations:

Renal/Hepatic insufficiency:
Reversible hypothalamic pituitary adrenal (HPA) axis of suppression following systemic absorption occurs as a result of the application of topical corticosteroids to large areas of the body or for prolonged periods of time, under occlusion or in patients with hepatic insufficiency

The pediatric population:

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

Only limited data are available on the safety of MANTAZOL 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.

Its use is not recommended in the childhood age group unless it is mandatory.

The Geriatric population:

There is no different posology recommended for geriatric patients. No dosage changes are necessary.

4.3. Contraindications

It is contraindicated when tuberculous or syphilitic processes is found 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 substance or to any of the excipients.

4.4. Special warnings and precautions for use

Specific additional treatment is required when used in skin diseases infected with bacteria.

Long-term or intensive application of topical glucocorticoids to a large area, especially under occlusion conditions, may increase the risk of systemic side effects.

Care should be taken when applying it to the face, groin area or armpits, and when using it in children, due to the risk of increased side effects.
In addition, the increase in systemic absorption in children should be considered.In applications to the face, care should be taken that MANTAZOL does not get into the eyes.

As with systemic glucocorticoids, glaucoma may develop with the use of local glucocorticoids (eg, after long-term high doses or application to a large area, occlusive dressing, or application to the skin around the eyes).

If MANTAZOL is applied to the genital areas, excipients may cause damage that reduces the effectiveness of latex products used in preventive methods such as liquid paraffin and soft paraffin condoms and diaphragms.

Cetostearyl alcohol in MANTAZOL may cause local skin reactions (eg contact dermatitis).

Cross-resistance has been seen between isoconazole and miconazole, econazole and tioconazole.

4.5. Interaction with other medicinal products and other forms of interaction

None so far known.

Additional information on special populations

No interaction studies have yet been conducted in the special population.

Pediatric population

Interaction studies have not yet been conducted in the pediatric population.

4.6. Pregnancy and lactation

General advise

Pregnancy category: C.

Women of childbearing potential / Birth control (Contraception)

There are no data regarding the use of isoconazole nitrate and diflucortolone valerate in women of childbearing potential

Animal experimental studies with glucocorticosteroids have shown reproductive toxicity (see selection 5.3.).

Pregnancy

A number of epidemiological studies suggest that there could possibly be an increased risk of oral clefts among newborns of women who were treated with systemic glucocorticosteroids during the first trimester of pregnancy. Data concerning topical glucocorticosteroid use during pregnancy are insufficient.

As a general rule, topical preparations containing corticoids should not be applied during the first trimester of pregnancy. The clinical indication for treatment with MANTAZOL must be carefully reviewed and the benefits weighed against the risks in pregnant and lactating women. In particular, large-area or prolonged use must be avoided.

Breast-feeding

It is not known whether isoconazole nitrate and diflucortolone valerate is excreted in breast milk.

A risk to breastfed children cannot be excluded.

The clinical indication for treatment with MANTAZOL should be carefully reviewed in lactating women and carefully weighed against the benefits and risks.
It should not be applied to the breasts of breastfeeding women. In large treatment areas, extended use or occlusive dressings should be avoided while breastfeeding.

Fertility

In a series of specific reproductive toxicity studies, isoconazole nitrate has not caused any side effects in any phase of the reproductive cycle.

4.7. Effects on ability to drive and use machines

There are no data regarding the effect of MANTAZOL on ability to drive and use machines

4.8. Undesirable effects

In clinical studies, the most observed adverse reactions at the application site were irritation and burning at the application site.

Undesirable effects regarding treatment in meta-analysis of clinical trials are listed in the following categories.
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).

General disorders and administration site conditions

Common: Irritation and burning at the application site
Uncommon: Application site erythema and dryness.
Unknown: Itching and vesicles at the application site

Skin and subcutaneous tissue diseases:
Uncommon: Striae
As with other glucocorticoids for topical application, the following adverse reactions may occur.

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.

Systemic effects due to absorption may occur when preparations containing glucocorticoids are administered.

Some adverse reactions are also possible in neonates (eg, decreased adrenal gland function, immunosuppression) when MANTAZOL is administered for a long time or in large areas during pregnancy or lactation in women.

Additional information on special populations:

Kidney/Liver failure:
Reversible hypothalamic-pituitary adrenal (HPA) axis following systemic absorption with high-potency, long-term, large-area, under-occlusion or use of topical corticosteroids in patients with concomitant hepatic impairment.
suppression occurs.

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

Only limited data are available on the safety of MANTAZOL 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 side effects

If you get any side effects, stated or not stated in the Patient Information Leaflet, talk to your doctor or pharmacist. Also, please report the side effects you have to Turkish Pharmacovigilance Center (TÜFAM) by either clicking to "Reporting Drug Side Effect" icon on www.titck.gov.tr or calling side effect reporting line via 0 800 314 00 08. By reporting the side effects you can help provide more information on the safety of this medicine.

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TÜFAM	Turkish Pharmacovigilance Center www.titck.gov.tr

If you experience any side effects not listed in this leaflet, please tell your doctor or pharmacist.

4.9. Overdose and treatment

Based on results from acute toxicity studies, no risk is expected following a single overdose to the skin (application over a large area under conditions of absorption) or accidental ingestion.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Potent (Group III) corticosteroid combination antifungal (imidazole derivative) 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 as against the causative organisms of *Erythrasma*.

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

5.2. Pharmacokinetic properties

- Isoconazole nitrate

Absorption:

Isoconazole penetrates rapidly into human skin and maximum drug levels 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 characterised as quantitatively most important metabolites.

Isoconazole is not metabolically inactivated in the skin.

Elimination:
In order to investigate the fate of isoconazole nitrate within the human organism, the percutaneously absorbed portion was too low. Therefore 0.5 mg of ^{3}H-labelled isoconazole nitrate were intravenously injected. Isoconazole is completely metabolised 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.

Linearity/non-linearity:

No data available

- Diflucortolone valerate:

Absorption:
Isoconazole does not influence penetration and percutaneous absorption of diflucortolone valerate. The portion of the corticosteroid which is percutaneously absorbed is low. Within four hours exposure time, less than 1 % of the topically applied MANTAZOL dose has been percutaneously absorbed.

Distribution:
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).

Biotransformation:
Diflucortolone valerate is partly hydrolysed in the skin to the likewise effective diflucortolone. 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.

Elimination:

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.

Linearity/non-linearity:

No data available

Pharmacokinetic / pharmacodynamic relation(s)
After topical application to rabbits higher levels of the antimycotic were obtained in the skin as compared to the corticosteroid-free preparation. This was interpreted as a retardation of percutaneous absorption as a consequence of the vasoconstrictive effect of the corticosteroid.

The concentration ratio between antimycotic and corticosteroid in the skin is increased as compared to a ratio of 10:1 present in isoconazole nitrate/diflucortolone valerate , 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 on isoconazole nitrate 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 MANTAZOL during pregnancy. The results of epidemiological studies are summarized under section “4.6 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 PROPERTIES

6.1. List of excipients

Liquid paraffin
Yellow soft paraffin
Polysorbate 60
Cetostearyl alcohol
Disodium EDTA
Sorbitan stearate
Deionized water

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at room temperature below 30 ° C.

6.5. Nature and contents of container

There are 15 g cream in aluminium tubes with the plastic screw cap.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Humanis Saglik A.S.
Istanbul/TURKEY

8. MANUFACTURER

Humanis Saglik A.S.
Karaagac Mah., Fatih Blv., No:32 Cerkezkoy Organize
Sanayi Bolgesi- Kapakli/Tekirdag/TURKEY

9. MARKETING AUTHORISATION NUMBER (S)

04337/5037/NMR/2017

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10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: Mar 18, 2019
Date of latest renewal:

11. DATE OF REVISION OF THE TEXT

12.03.2020