SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IMPETEX 0.1% + 1% cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 g contains:

Active substance:

Diflucortolone valerate 1 mg

Chlorquinaldol 10 mg

Excipient(s):

Stearyl alcohol 80 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cream

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMPETEX is indicated for initial and intermittent treatment of bacterially and / or mycotically infected skin diseases as long as inflammatory concomitant symptoms predominate and in which a cream is indicated.

- Bacterially and / or mycotically infected eczema (such as nummular, seborrhoeic and dyshidrotic eczema), eczema in varicose syndrome (but not applied directly onto lower limb ulcus); prominent reaction with occurrence of skin vesicles and pustules due to hypersensitivity to bacterial infection (bacterid), eczematid
- Skin infections, such as pyoderma (folliculitis, impetigo) and erythrasma
- Dermatomycoses (tinea, candidiasis, pityriasis versicolor)

IMPETEX is also used to prevent the above mentioned bacterial and mycotic infections in inflammatory and allergic skin diseases.

4.2 Posology and method of administration

Dosage

At the beginning of treatment, IMPETEX is applied in a thin layer to the diseased skin 2 - sometimes 3 times a day. When there is an improvement in the disease setting, it is frequently sufficient to apply once a day.

Infants, children and adults should not continue the treatment for a period longer than 3 weeks.

IMPETEX is not recommended for use in the pediatric age group unless absolutely necessary.

Method of administration
It is used by applying topically on the diseased skin.

4.3 Contraindications
Tuberculous or syphilitic processes at the treated area; virosis (e.g. varicella, herpes zoster), rosacea, perioral dermatitis and post-vaccination skin reactions at the treated area.

Known hypersensitivity to any of the ingredients.

4.4 Special warnings and precautions for use
For facial applications, care should be taken not to get IMPETEX in the eyes.

Application of topical corticosteroids on large areas for long period of time significantly increase the adverse events risk especially under conditions of occlusive dressing.

As with the systemic corticoids, application of local corticoids (such as application at high dose for a long period of time or on a large area, to the occlusive dressing or orbital skin of eye) may lead to glaucoma.

This medicinal product contains stearyl alcohol. May cause local skin reactions (such as contact dermatitis).

4.5 Interaction with other medicinal products and other forms of interaction
None known.

4.6 Fertility, pregnancy and lactation
General advice
Pregnancy category: C.

Pregnancy
Glucocorticoids have demonstrated reproductive toxic effect in experimental animal studies (see 5.3 Preclinical safety data).

Several epidemiologic studies suggest that there may be an increased risk of cleft palate in infants of women treated with systemic glucocorticoids during the first trimester of their pregnancy. Cleft palate is a rare developmental disorder and if systemic glucocorticoids are teratogenic, this means an increase of 1 or 2 cases per 1000 women receiving treatment during their pregnancy. However, there is no adequate data for use of topical glucocorticoids during

pregnancies, still as the systemic effects of topical glucocorticoids are very low, a lower rate should be expected.

As a general rule, topical preparations containing corticoid should not be used during first trimester of pregnancy. Clinical indication of treatment with IMPETEX should be cautiously reviewed and evaluated for benefit and risk in pregnant women. Especially treatment of large areas should be avoided.
Studies conducted in animals are insufficient in terms of effects on pregnancy /and-or/ embryonic/foetal development /and-or/ parturition /and-or/ postnatal development (see section 5.3.). The potential risk for humans is unknown.

IMPETEX should not be used during pregnancy unless clearly necessary.

Lactation
It should not be applied to the breasts of breastfeeding women.

4.7 Effects on ability to drive and use machines
There are no data showing that IMPETEX has an effect on ability to drive and use machines.

4.8 Undesirable effects
In rare cases, local symptoms such as itching, burning, erythema or vesiculation may occur during treatment with IMPETEX.

The incidence rates of undesirable effects from clinical trials were defined as follows:
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), unknown (cannot be estimated from available data).

When topical preparations containing corticoids are applied over large areas (10% or more of the body surface) or for prolonged periods (longer than 4 weeks), the following side effects may occur: skin atrophy, teleangiectasias, striae, acne-like changes and systemic effects due to corticoid resorption.

As with other corticoids for topical application, in rare cases folliculitis, hypertrichosis, perioral dermatitis, skin discoloration and allergic reactions to the ingredients may occur. Adverse effects may also occur in newborn when IMPETEX is applied for a long period of time or on large areas during pregnancy or lactation (such as reduction in adrenal function caused by administrations during the last weeks of pregnancy).

<u>Reporting of suspected adverse reactions</u>

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 via the national reporting system.

4.9 Overdose

Results of acute toxicity studies have shown no acute toxicity risk following single overdose of product (administration on a large area under conditions suitable for absorption) or accidental oral use.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: MTA (Topical External Creams)
ATC code: D07BC04

Diflucortolone valerate prevents inflammation in inflammatory and allergic conditions of skin and eases the subjective complaints like pruritus, burning or pain.

Capillary dilatation, intercellular edema and tissue infiltration is reversed; proliferation is suppressed. This situation helps the inflammated skin surfaces to gradually improve.
Chlorquinaldol inhibits the growth of bacteria, yeasts, dermatophytes and moulds.

5.2 Pharmacokinetic properties

- Diflucortolone valerate

For diflucortolone valerate to be effective, it must be separated from the formulation and penetrate the skin. *In vitro* studies on human skin have shown that diflucortolone valerate penetrates rapidly into the horn layer. A maximum corticosteroid level of approximately 500 mcg/ml (i.e. 1000 mcmol/l) was measured in the horn layer 4 hours after application of the cream. The concentration in the horn layer decreased from about 10 to 1.5-2 power from distal to proximal. Concentrations in living skin after application to peeling skin (as a model of diseased skin) were significantly higher than after application to healthy skin.

Diflucortolone valerate is partially hydrolyzed in the skin to diflucortolone with the same activity. The amount of corticosteroid absorbed percutaneously is low. Less than 1% of the topically applied diflucortolone valerate and chlorquinaldol combination was absorbed percutaneously after 4 hours of application.

Diflucortolone valerate entering 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 were also detected in plasma. Diflucortolone is eliminated from plasma with a half-life of 4-5 hours and its metabolites with a half-life of

approximately 9 hours (half-life after i.v. injection) and 75% is excreted in urine and 25% in feces.

- Chlorquinaldol

Chlorquinaldol is absorbed percutaneously through intact skin in very small amounts. After application to diseased skin, the rate of systemic effects is thought to be less than 10% of the administered dose.

After penetrating the organism, chlorquinaldol is rapidly and almost completely excreted as glucuronide in the urine. Since the conversion of chlorquinaldol to its excretable metabolites occurs only by conjugation and not by oxidation reactions, it is unlikely to interact with concomitant P450 system enzymes.

5.3 Preclinical safety data

Effect of diflucortolone valerate was as the typical glucocorticoids with the systemic tolerance studies performed following repeated dermal and subcutaneous administrations. From these results, side effects other than typical glucocorticoid effects are not expected to occur following excessive therapeutic use of the combination of diflucortolone valerate and chlorquinaldol on large areas and/or occlusive dressings.

Based on results from repeated dose systemic tolerance studies, isoconazole nitrate is not expected to have a systemic effect in combination therapy with diflucortolone valerate and chlorquinaldol.

Embryotoxicity studies with the combination of diflucortolone valerate and chlorquinaldol gave results typical for glucocorticoids, i.e. the appropriate test system showed embryolethal and/or teratogenic effects. In light of these findings, the prescription of IMPETEX during pregnancy requires special caution. Results of epidemiological studies are summarized in section named "4.6 Pregnancy and Lactation". No embryotoxic/teratogenic effects were observed following dermal administration of the maximal use dose of chlorquinaldol.

No data on the mutagenic potential of diflucortolone valerate or isoconazole nitrate have been found *in in vitro* and *in vivo* experiments investigating gene mutations in bacterial and mammalian cells, as well as chromosome and genome mutations.

Specific tumorigenicity studies have not been performed with diflucortolone valerate or isoconazole nitrate. Based on the pharmacodynamic effect, lack of evidence of genotoxic potential, structural features and 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 in dermal administration of IMPETEX, it is not expected to have influence on tumor formation.

Based on the results of local tolerance studies following repeated dermal administration in combination with diflucortolone valerate and chlorquinaldol alone, no dermal changes are expected with combination therapy of diflucortolone valerate and chlorquinaldol, except for side effects known for glucocorticoids.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyoxyethylene stearate
Stearyl alcohol
Liquid paraffin
White vaseline
Carboxyvinyl polymer
Sodium hydroxide pellets
Disodium edetate dihydrate
Purified water

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at room temperature below 30°C.

6.5 Nature and contents of container

10 g and 15 g aluminum tube with HDPE cap, printed on the outside and coated with epoxy phenol lacquer on the inside

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

221/13

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 10/14/2009
Renewal of the authorization:

10. DATE OF REVISION OF THE TEXT