TINATRIM

NAME OF THE MEDICINAL PRODUCT

Clotrimazole, 10 mg/g, cream

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 gram of cream contains 10 mg of clotrimazole.

Excipients

Chlorocresol, Cetomacrogol 1000, Cetostearyl alcohol, White soft paraffin, (Silkolene 394)/(Rajell-UP12AD3), Liquid paraffin/ Mineral oil, Sodium dihydrogen, Phosphate, Dihydrate (Sodium acid phosphate)/ Monobasic, Sodium phosphate, Dihydrate phosphoric acid (10% w/v solution to pH 4.8-5.2) or Sodium hydroxide (4% w/v solution to pH 4.8-5.2), Purified water

PHARMACEUTICAL FORM

Smooth, white mass with homogeneous consistence.
or
Smooth white homogenous cream with the odour of benzyl alcohol.

CLINICAL INFORMATION

Indications

For the topical treatment of:

- infections due to superficial dermatophytes
- fungal infections due to *Candida* and other sensitive pathogens as *Trichomonas, Staphylococci* and *Bacteroides* but not against *Lactobacilli*

Cutaneous solution is particularly suitable for infections covering large and/or hairy areas.
The following additional indications are also present in some local markets:

- dermal fungal infections
- yeast infections of the skin and mucous membranes of external sex organs (labia, foreskin and glans) caused by *Candida vulvitis* and *Candida balanitis*
- feet and skin folds mycoses
- athlete's foot
- thrush, moulds
- pityriasis versicolor caused by *Malassezia furfur (Pityrosporum orbiculare* or *Pityrosporum ovale)*
- ringworm (tinea) infections
- paronychia
- erythrasma
- fungal nappy rash
- mycoses with secondary pyoderma
- fungal infections of the outer ear (otitis externa)
- other infections caused by agents sensitive to clotrimazole.

Dosage and Administration

Cream, cutaneous solution and cutaneous spray should be applied on clean dry areas of affected skin (to be washed by neutral pH soap). If applied to the feet they should be thoroughly washed, dried and then the cream/ cutaneous solution/ cutaneous spray should be applied between the toes.
Patients should notify their physician if there is no improvement after 4 weeks of treatment.

Route of Administration

For cutaneous use.

Adults and children over 12 years of age

Cream should be applied to the affected area two or three times daily.
To prevent relapse, treatment should be continues for at least two weeks after disappearance of all signs of infection.

The following additional Dosage and Administration information is also present in some local markets:
The duration of treatment depends on the severity of the disease, its location and the treatment efficacy.
Suggested treatment duration:

- dermatophytes infections - at least one month
- *Candida* infection - at least two weeks

The duration of treatment will vary according to individual circumstances but should not be less than 3 weeks. To prevent recurrence of the infection it is important to continue treatment for 1-2 weeks after disappearance of all signs of infection.
If symptoms do not improve after 7 days of treatment medical advice should be sought.

Children

There are no relevant data available.

Elderly

There are no relevant data available.

Renal impairment

There are no relevant data available.

Hepatic impairment

There are no relevant data available.

Contraindications

Clotrimazole is contraindicated in:

- hypersensitivity to clotrimazole or any excipients of product.

Warnings and Precautions

Avoid contact with eyes and do not swallow.
All possibly infected areas should be treated at the same time.
Excipients
Due to the content of cetostearyl alcohol, this medicinal product may cause local skin reaction (e.g. contact dermatitis).

Interactions

Contraceptives
Laboratory tests have suggested that, when used together, this product may cause damage to latex contraceptives. Consequently the effectiveness of such contraceptives may be reduced. Patients should be advised to use alternative precautions for at least five days after using this product.
Tacrolimus, Sirolimus
Concomitant medication with vaginal clotrimazole and oral tacrolimus (FK- 506; immunosuppressant) might lead to increased tacrolimus plasma levels and similarly with sirolimus. Patients should thus be thoroughly monitored for symptoms of tacrolimus or sirolimus overdosage, if necessary by determination of the respective plasma levels.

Pregnancy and Lactation

Fertility

No human studies of the effects of clotrimazole on fertility have been performed, however, animal studies have not demonstrated any effects of the drug on fertility.

Pregnancy

There are limited amount of data from the use of clotrimazole in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of clotrimazole during the first trimester of pregnancy.

Lactation

Available pharmacodynamic/toxicological data in animals have shown excretion of clotrimazole/metabolites in milk. Breast-feeding should be discontinued during treatment with clotrimazole.

Ability to perform tasks that require judgement, motor or cognitive skills
The medication has no or negligible influence on the ability to drive or use machinery.
Adverse Reactions
Clinical Trial Data
Not relevant for this product.
Post Marketing Data
Adverse reactions are ranked under headings of frequency using the following convention:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).
Immune system disorders
Not known: allergic reaction (with symptoms such as urticaria, dyspnoea, hypotension and syncope)
Skin and subcuteaneous tissue disorders
Not known: pruritus, rash, blisters, skin exfoliation, discomfort/pain, oedema, burning, irritation, erythema, stinging
Overdosage
Symptoms and signs
Overdose symptoms: dizziness, nausea, vomiting.
Treatment
In the event of accidental oral ingestion, routine symptomatic measures should be performed.
Clinical Pharmacology
Pharmacodynamics
Pharmacotherapeutic group
Antifungal drugs for topical use, imidazole and triazole derivatives.
ATC Code
D01AC01
Mechanism of action and pharmacodynamic effects
Clotrimazole inhibits growth and division of microorganisms and depending on the concentration it can exert fungistatic or fungicidal action. The mechanism of clotrimazole action involves change in the permeability of cellular membranes exerted through interference with ergosterol synthesis, as well as binding with phospholipids in the cellular walls of the fungi.
Clotrimazole inhibits the synthesis of proteins, fats, DNA and polysaccharides, damages the cellular nucleic acids and accelerates the excretion of potassium. It may also inhibit the activity of oxidative and peroxidative enzymes and the biosynthesis of triglycerides and phospholipids in the fungi. Higher concentration of clotrimazole produces cellular membrane damage via mechanisms independent of the synthesis of sterols. Clotrimazole prevents transformation of *Candida albicans* blastospores into an invasive mycelium form. Changes of cellular membrane activity result in cell death and this depends on the exposure of microbes to the medicinal product.
Spectrum of activity
Clotrimazole is characterised by a broad spectrum of antimycotic and antibacterial activity. It inhibits the development and destroys:
- dermatophytes *(Epidermophyton floccosum, Microsporum canis, Trichophyton mentagrophytes, Trichophyton rubrum),*
- yeasts *(Candida sp., Cryptococcus neoformans),*
- dimorphic fungi (*Coccidioides immitis, Histoplasma capsulatum, Paracoccidicides brasiliensis)*
- and protozoa *(Trichomonas vaginalis).*

It also acts against some Gram-positive bacteria.
In addition to its antimycotic action, clotrimazole also acts on, gram-positive microorganisms (streptococci/staphylococci/ Gardnerella vagiinalis) and gram-negative microorganisms (Bacteroides). It has no effect on Lactobacilli.
In vitro , clotrimazole inhibits the multiplication of Corynebacteria and gram-positive cocci – with the exception of enterococci – in concentrations of 0.5 – 10 μg/ml substrate.
In vitro clotrimazole has a broad spectrum of fungistatic and fungicidal activity. Its effects on the mycelium of dermatophytes (*Trichophyton, Microsporum, Epidermophyton*) are similar to the effects of griseofulvin, and its effects on budding fungi (*Candida*) is similar to the activity of polyenes (amphotericin B and nystatin).
Clotrimazole concentration below 1 μg/ml inhibits the development of most strains of *Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum* and *Microsporum canis.*
Concentration of 3 μg/ml inhibits the development of the majority of other pathogens: *Pitorosporum orbiculare, Aspergillus fumigatus, Candida species* including *Candida albicans,* some strains of *Staphylococcus aureus, Streptococcus pyogenis,* and also some strains of *Proteus vulgaris* and *Salmonella.* Clotrimazole acts against *Sporotrix, Cryptococcus, Cefalosporium* and *Fusarium.*
Concentrations over 100 μg/ml are effective against *Trichomonas vaginalis*.
Clotrimazole-resistant fungi are extremely rare; only isolated strains of *Candida guilliermondi* have been described.
Currently there are no reports on the resistance among clotrimazole sensitive fungi after passage of *Candida albicans* and *Trichophyton mentagrophytes*. No resistance to clotrimazole was observed in *C. albicans* strains, which were resistant to polyene antibiotics following chemical mutation.

Pharmacokinetics

Absorption and distribution

Pharmacokinetic investigations after dermal application have shown that clotrimazole is practically not absorbed from the intact or inflamed skin into the human blood circulation. The resulting peak serum concentrations of clotrimazole were below the detection limit of 0.001 μg/ml, reflecting that clotrimazole applied topically dose not lead to measurable systemic effects or side effects.

Metabolism and elimination

Clotrimazole is metabolised in the liver to inactive substances excreted in urine and faeces.

Clinical Studies

Not relevant for this product.

NON-CLINICAL INFORMATION

There are no pre-clinical data of relevance to the prescriber, which are additional to the information included in other sections.

PHARMACEUTICAL INFORMATION

Shelf-Life

As registered locally.

Storage

As registered locally.

Nature and Contents of Container

As registered locally.

Incompatibilities

There are no relevant data available.

Use and Handling

Cutaneous solution and spray should not be used near flame. Do not smoke or open flames whenever applied.

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Manufactured By:
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