

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TERBISIL® 1% spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

1 ml spray contains 10 mg terbinafine hydrochloride.

Excipients:

Contains propylene glycol (1.5 g).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution.

Clear, particle-free solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Tinea pedis
- Tinea corporis/cruris
- Cutaneous candidiasis
- Pityriasis (Tinea) versicolor

4.2. Posology and method of administration

Posology:

Unless otherwise prescribed by the doctor, in adults (>16);

TERBISIL®, is applied once or twice daily depending on the indication. Cleanse and dry the affected areas before applying TERBISIL®. Apply a sufficient amount of spray to wet the infected area thoroughly, and to cover the lesional skin and surrounding area. In cases of intertrigenous infections (under the breasts, interdigital, intergluteal or inguinal) the skin may be covered with a sterile compress after application of the solution, especially at night.

For manipulation of the spray pump the bottle can be held in the upright or inverted position.

When using TERBISIL® for the first time, the patient will need to depress the actuator a few times (usually up to 3 actuations) for an effective spray.

Tinea corporis/cruris:
Approximate durations of treatment:

Tinea pedis:

Cutaneous candidiasis: Once a day for one week.

Pityriasis versicolor: Once a day for one week.

Once or twice a day for one week.

Twice a day for one week.

Frequency and duration of administration:

Relief of clinical symptoms usually occurs within a few days. Irregular use or premature discontinuation of treatment carries the risk of recurrence. If there are no signs of improvement after two weeks, the diagnosis should be reviewed.

Method of application

For topical use.

Additional information on special populations

Renal / Hepatic Failure:

There is no data on dosage adjustment in patients with renal and hepatic failure.

Pediatric population

The safety of use in children has not been demonstrated.

The experience with terbinafine in children under 16 years of age is limited, its use is therefore not recommended.

Geriatric population:

There is no evidence to suggest that elderly patients (65 years or older) require different dosages or experience side effects different from those in younger patients.

4.3. Contraindications

Known hypersensitivity to terbinafine or any of the excipients contained in TERBISIL®.

4.4. Special warnings and precautions for use

It may cause toxic epidermal necrolysis. In addition, skin irritation and sensitivity can be observed.

It should be used with caution in patients with lesions as the alcohol contained in TERBISIL® may be irritating.

TERBISIL® is for external use only. It may be irritating to the eyes. In case of accidental contact with the eyes, rinse eyes thoroughly with plenty of water. If any symptoms develop, consult a physician.

TERBISIL® should not be used on the face.

In case of accidental inhalation, consult a physician if any symptoms develop.

TERBISIL® contains propylene glycol, which may cause skin irritation.

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

No drug interaction with TERBISIL® has been reported so far.

Additional information on special populations

No clinical interaction study has been performed for special populations.

Pediatric population No interaction study has been performed in pediatric population. It should not be used in patients under 16 years of age due to lack of enough clinical experience.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category B.

Women with childbearing potential / Contraception

There are no data supporting special recommendations for women of childbearing potential.

Pregnancy

Clinical data on exposure to terbinafine during pregnancy is not available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (See section 5.3).

Since the clinical experience in pregnant women is limited, TERBISIL® should not be used during pregnancy unless the expected benefits are greater than the possible risks.

Lactation

Terbinafine is excreted in breast milk to the extent that the therapeutic doses of TERBISIL® administered to breastfeeding women may cause effects on the breastfed child.

Infants must also not be allowed to come into contact with any treated skin, including the breast. TERBISIL® should not be used when breastfeeding.

Fertility

No effects of terbinafine on fertility have been seen in animal studies and there is no data suggesting that fertility may be affected in humans.

4.7. Effects on ability to drive and use machines

TERBISIL® has no influence on the ability to drive and use machines.

4.8. Undesirable effects

Local symptoms such as pruritus, skin exfoliation, application site pain, application site irritation, pigmentation disorder, skin burning sensation, erythema and scab may occur at the site of application. These minor symptoms must be distinguished from hypersensitivity reactions including rash which are reported in sporadic cases and require discontinuation. In case of accidental contact with the eyes terbinafine may be irritating to the eyes. In rare cases the underlying fungal infection may be aggravated.

Undesirable effects from clinical trials are listed by MedDRA system organ class. In each system organ class, undesirable effects are listed according to frequency and the most common reactions are in the first order. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Furthermore, the frequency category corresponding to each undesirable effect is based on the following convention (CIOMS III).

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 ($< 1/10,000$); not known (cannot be estimated from the available data)

In addition, some undesirable effects have been obtained from spontaneous case reports based on post-marketing experience with terbinafine and cases in the literature.

Because these reactions are reported voluntarily by a population whose size is unclear, it is not

possible to reliably calculate their frequency, so these are classified as "frequency unknown". These undesirable effects are listed in the same way as undesirable effects from clinical trials.

Immune system disorders

Not known: Hypersensitivity*

Eye disorders

Rare: Eye irritation

Skin and subcutaneous tissue disorders

Common: Skin exfoliation, pruritus

Uncommon: Skin lesion, scab, skin disorder, pigmentation disorder, erythema, skin burning sensation

Rare: Dry skin, dermatitis contact, eczema

Not known: Skin rash*

General disorders and administration site conditions

Uncommon: Pain, application site pain, application site irritation

Rare: Condition aggravated

* Based on post marketing experience

Reporting of suspected adverse reactions

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also 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

The low systemic absorption of topical terbinafine renders overdosage extremely unlikely. However, accidental ingestion of the contents of one 30 ml bottle of TERBISIL® which contains 300 mg terbinafine hydrochloride, is comparable to ingestion of one TERBISIL® 250 mg tablet (adult oral unit dose).

Should a larger amount of TERBISIL® be inadvertently ingested, adverse effects similar to those observed with an overdosage of TERBISIL® tablets are to be expected. These include headache, nausea, epigastric pain and dizziness.

In case of accidental oral ingestion, the 31%v/v alcohol content of TERBISIL® has to be considered.

The recommended treatment of overdosage consists of eliminating the active substance, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antifungal for topical use

ATC Code: D01AE15

Terbinafine is an allylamine which has a broad spectrum of antifungal activity in fungal infections of the skin caused by dermatophytes such as *Trichophyton* (*T. rubrum*, *T. mentagrophytes*, *T. verrucosum*, *T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*. At low concentrations terbinafine is fungicidal against dermatophytes and moulds. The activity against yeasts is fungicidal (e.g. *Pityrosporum orbiculare* or *Malassezia furfur*) or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system.

5.2. Pharmacokinetic properties

General properties:

Terbinafine is a white to almost white powder. It is soluble in methanol and ethanol, whereas very slightly or slightly soluble in water. It is also slightly soluble in alcohol. Protect from light.

Absorption

Less than 5% of the dose is absorbed after topical application to humans; systemic exposure is thus very slight.

Distribution

Following topical administration, the levels of blood terbinafine are very low. Therefore, terbinafine metabolism cannot be examined after topical application.

Oral terbinafine, however, is strongly bound to plasma proteins (99%). It is rapidly diffuses through the skin and concentrates in the lipophilic stratum corneum. Oral terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and parts of the skin rich in sebaceous glands. There is also evidence that oral terbinafine is distributed into the nail plate within a few weeks after commencing therapy.

Biotransformation:

Following topical administration, the levels of blood terbinafine are very low. Therefore, the biotransformation of terbinafine cannot be examined after topical application.

Oral terbinafine is rapidly metabolised by the CYP-isoenzymes, mainly by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19.

Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. The elimination half-life is 17 hours. There is no evidence of accumulation in the plasma.

Elimination:

No age-dependent pharmacokinetic changes have been observed in steady state plasma concentrations of oral terbinafine but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in higher blood levels of terbinafine.

Linearity / Non-linearity:

This information is not available since it is applied topically.

5.3. Preclinical safety data

In long-term studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats at the highest dose level, 69mg/kg a day, an increased incidence of liver tumours was observed in males. The changes, which may be associated with peroxisome proliferation, have been shown to be species-specific since they were not seen in the carcinogenicity study in mice or in other studies in mice, dogs or monkeys.

During the studies of high dose oral terbinafine in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic effect level was 50mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after drug discontinuation. They were not associated with histological changes.

A standard battery of in vitro and in vivo genotoxicity tests revealed no evidence of a mutagenic or clastogenic potential for the drug.

No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

6. PHARMACEUTICAL PROPERTIES

6.1. List of Excipients

Cetomacrogol 1000
Propylene glycol
Ethanol (96%)
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 and in its packaging.

6.5. Nature and contents of container

It is available as a 30 ml colored glass bottle in a box.

6.6. Special precautions for disposal of waste materials derived from the medicinal product and other handling

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 AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST LICENSE/RENEWAL OF THE LICENSE

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]