

SUMMARY OF PRIDUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TERBISIL® PLUS 1% + 0.1% Cream

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substances:

- Each 1 g of cream contains:
 - Terbinafine Hydrochloride 10 mg
 - Mometasone Furoate 1 mg

Excipients:

- **Cetyl Alcohol** 40 mg
- **Stearyl Alcohol** 40 mg
- For other excipients, see section 6.1

3. PHARMACEUTICAL FORM

Cream

A bright, white, homogeneous cream

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

TERBISIL® PLUS is indicated for the initial and adjunctive treatment of superficial skin fungal infections associated with eczema-like reactions, including:

- Tinea pedis (Athlete's foot)
- Tinea corporis (Ringworm of the body)
- Tinea cruris (Jock itch)
- Cutaneous candidiasis
- Pityriasis versicolor

4.2 Posology and Method of Administration

Dosage / Frequency and Duration of Application:

Unless otherwise directed by your doctor, it may be applied once daily in adults and adolescents over 16 years old, depending on the condition.

Clinical symptoms typically improve within a few days. The treatment duration should not exceed 10 days.

Particularly for lesions in the groin and genital area, the treatment duration should be closely monitored.

Irregular use or early discontinuation may increase the risk of recurrence.

If no improvement is seen within two weeks after treatment, consult your doctor.

Method of Application:

For topical use only.

Before applying TERBISIL® PLUS, clean and dry the affected area of the skin. Apply a thin layer of the cream to the affected area and surrounding skin, and gently rub it in.

Special Population Information:

Renal / Hepatic Insufficiency:

No studies have been conducted with TERBISIL® PLUS in patients with renal or hepatic insufficiency.

Pediatric Population:

The safety and efficacy of the combination of Mometasone Furoate and Terbinafine Hydrochloride in children are not known. Therefore, TERBISIL® PLUS is not recommended for use in children under 16 years of age.

It is not recommended for use in infants and young children unless absolutely necessary.

Geriatric Population:

The safety and efficacy of TERBISIL® PLUS in elderly patients have not been studied.

4.3. Contraindications

TERBISIL® PLUS is contraindicated in patients who are hypersensitive to Terbinafine Hydrochloride, Mometasone Furoate, or any other ingredients of the product (see Section 6.1).

TERBISIL® PLUS is also contraindicated in patients with:

- Facial rosacea, acne vulgaris, perioral dermatitis,
- Perianal and genital pruritus,
- Bacterial infections (e.g., impetigo), viral infections (e.g., herpes simplex, herpes zoster, chickenpox),
- Tuberculosis, syphilis, or post-vaccination reactions in the treatment area.

4.4. Special Warnings and Precautions for Use

TERBISIL® PLUS is for topical use only.

It should be avoided from coming into contact with the eyes, as it may increase the risk of elevated intraocular pressure. In case of accidental eye contact, rinse the eye thoroughly with water. If any symptoms develop, consult a physician.

Because TERBISIL® PLUS contains a corticosteroid, it is not recommended for use on

atrophic skin, cutaneous ulcers, acne vulgaris, sensitive skin areas, or in cases of perianal and genital pruritus. It should also be avoided on open wounds and mucous membranes.

If irritation or sensitivity occurs during treatment with TERBISIL® PLUS, discontinue use and begin appropriate therapy. It should be used with caution in patients who have had allergic-type reactions to other topical or oral corticosteroids.

TERBISIL® PLUS should not be used for prolonged periods of time, regardless of age. Especially with large skin surface areas, intertriginous areas, under occlusive bandages, or with prolonged use, local and systemic toxicity may occur.

The systemic absorption of potent topical corticosteroids can lead to reversible hormonal effects (suppression of the hypothalamic-pituitary-adrenal axis, symptoms of Cushing's syndrome), hyperglycemia, and glucosuria in some patients when treatment is discontinued.

Rarely, symptoms may appear upon discontinuation of corticosteroids. In such cases, systemic corticosteroid replacement therapy may be required.

Due to a larger skin surface area relative to body weight, children may be more sensitive to hormonal effects (HPA axis suppression and Cushing's syndrome) induced by topical corticosteroids than adults.

The use of topical steroids in children should be limited to the smallest effective dose to ensure the success of treatment. Chronic corticosteroid therapy may affect growth and development in children.

Patients should be warned not to smoke or approach open flames while using the product, as it poses a risk of serious burns. TERBISIL® PLUS can easily ignite clothing, bedding, and dressings, leading to a significant fire hazard. Washing clothes and bedding may reduce but not completely eliminate this risk.

Candidiasis:

It is not recommended to use TERBISIL® PLUS with acidic pH soaps, as they provide a suitable growth environment for Candida species.

TERBISIL® PLUS should not be used ophthalmically, including on the eyelids, as it can rarely cause glaucoma or subcapsular cataracts.

Visual disturbances, which may include blurred vision or other visual impairments, have been reported with the use of systemic and topical (intranasal, inhaled, and intraocular) corticosteroids. If a patient experiences symptoms such as blurred vision or other visual disturbances after using systemic and topical corticosteroids, referral to an ophthalmologist should be considered to evaluate the potential causes of visual disturbances, such as cataracts, glaucoma, or central serous chorioretinopathy (CSCR).

Terbinafine Hydrochloride use may lead to toxic epidermal necrolysis. Skin irritation and sensitivity may also occur.

Proper hygienic measures are essential for the success of treatment with TERBISIL® PLUS. In cases of fungal infections on the feet, wash and thoroughly dry between the toes, and change socks daily.

TERBISIL® PLUS contains Cetyl Alcohol and Stearyl Alcohol, which may cause local skin reactions (e.g., contact dermatitis).

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

No known interactions.

Special Population Information

No studies have been conducted in this regard.

Pediatric Population

No studies have been conducted in this regard.

4.6. Pregnancy and Lactation

General Advice:

Pregnancy Category: C

Women of Childbearing Potential/Contraception:

There is no data available regarding the effects of topically applied Mometasone Furoate and Terbinafine Hydrochloride on women of childbearing potential or on contraception.

Pregnancy:

There is insufficient data regarding the use of TERBISIL® PLUS in pregnant women. Studies in animals have shown reproductive toxicity with Mometasone Furoate, but the potential risk to humans is unknown.

TERBISIL® PLUS should not be used during pregnancy unless absolutely necessary.

There are no studies showing teratogenic effects of topically applied corticosteroids in pregnant women. Therefore, these medications should be used during pregnancy only when the potential benefits outweigh the risks. Application during pregnancy should not cover large areas of the skin, and treatment should not be prolonged.

Information on the safety of TERBISIL® PLUS in pregnant women is limited.

Topical corticosteroids should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the fetus. Medications in this class should not be used in large amounts or for long periods in pregnant women.

Lactation:

It is unknown whether Mometasone Furoate, one of the active ingredients in TERBISIL® PLUS, is excreted in human breast milk when applied topically. However, Terbinafine does pass into breast milk. Terbinafine Hydrochloride, the other active ingredient in TERBISIL® PLUS, is excreted in breast milk in amounts that could affect the nursing infant.

TERBISIL® PLUS should not be used during breastfeeding.

Additionally, infants should not come into contact with treated skin areas, including the breast.

Fertility:

The effects on fertility are not known. Mometasone Furoate has shown no mutagenic potential in genetic toxicity studies (Ames test, mouse lymphoma test, and micronucleus test). In animal studies, Terbinafine did not affect fertility, and there is no evidence to suggest that fertility may be impacted in humans.

4.7. Effects on Ability to Drive and Use Machines:

No adverse effects on the ability to drive or operate machinery have been reported.

4.8. Undesirable Effects:

Local symptoms such as pruritus, skin exfoliation, pain at the application site, irritation at the application site, pigmentation disorders, burning sensation, erythema, crusting, etc., may occur. These minor symptoms should not be confused with hypersensitivity reactions, including skin rashes, which have been sporadically reported and may require discontinuation of treatment.

In case of accidental eye contact, TERBISIL® PLUS may cause irritation. Rarely, an underlying fungal infection may worsen.

The following frequency groups have been used:

- 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 ($< 1/10,000$)
- Unknown (cannot be estimated from the available data)

Infections and Infestations:

- Very rare: Folliculitis, alopecia
- Unknown: Infection, furunculosis

Immune System Disorders:

- Unknown: Hypersensitivity

Nervous System Disorders:

- Very rare: Burning sensation
- Unknown: Paresthesia

Eye Disorders:

- Rare: Eye irritation
- Unknown: Blurred vision

Skin and Subcutaneous Tissue Disorders:

- Common: Skin exfoliation and pruritus
- Uncommon: Skin lesions, crusting, skin discomfort, pigmentation disorders, erythema, burning sensation on the skin
- Rare: Dry skin, contact dermatitis, eczema
- Unknown: Skin rash, hirsutism, striae, acne, and skin atrophy

General Disorders and Application Site Conditions:

- Uncommon: Pain, pain at the application site, irritation at the application site
- Rare: Worsening of skin condition
- Unknown: Reactions at the application site

Rare local adverse reactions reported with topical dermatologic corticosteroids:

Dryness, irritation, dermatitis, perioral dermatitis, skin maceration, miliaria, and telangiectasia.

Children:

Due to the larger skin surface area relative to body weight, children may be more sensitive to hormonal effects (HPA axis suppression and Cushing's syndrome) induced by topical corticosteroids than adults.

The use of topical steroids in children should be limited to the smallest effective dose to ensure the success of treatment. Chronic corticosteroid therapy may affect growth and development in children.

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 and Treatment

No cases of overdose have been reported following topical application.

Excessive and prolonged use of topical corticosteroids can suppress pituitary-adrenal function, leading to secondary adrenal insufficiency. In such cases, treatment should be discontinued. If HPA axis suppression occurs, the drug should be stopped, the frequency of application reduced, or a lower-potency steroid should be considered. In case of overdose, symptomatic supportive treatment should be administered as needed. Symptoms of acute hypercortisolism are almost completely reversible.

If necessary, electrolyte imbalances should be corrected. In cases of chronic toxicity, corticosteroids should be gradually withdrawn.

The likelihood of overdose from a cream containing terbinafine, due to its low systemic absorption, is extremely low. Accidentally ingesting 20 grams of TERBISIL® PLUS cream (containing 200 mg of terbinafine hydrochloride) is comparable to taking a 250 mg terbinafine tablet (the typical adult oral dose). However, if a higher amount of terbinafine-containing cream is ingested orally, side effects similar to those observed in terbinafine tablet overdose are expected. These side effects may include headache, nausea, epigastric pain, and dizziness.

The recommended treatment for overdose, based on elimination principles, primarily involves administering activated charcoal and, if necessary, symptomatic supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Other antifungals for topical use, combinations

ATC Code: D01AE20

TERBISIL® PLUS combines Mometasone Furoate, which has anti-inflammatory and antipruritic effects, with Terbinafine Hydrochloride, a potent topical antifungal agent. Terbinafine Hydrochloride has a broad antifungal spectrum of activity against dermatophytes causing fungal skin infections such as Tinea pedis, Tinea corporis, Tinea cruris, cutaneous candidiasis, and pityriasis versicolor. At low concentrations, terbinafine exhibits fungicidal activity against dermatophytes, molds, and some dimorphic fungal species. Its effect against yeast fungi varies depending on the species and can be either fungicidal (e.g., *Candida albicans*, *Pityrosporum orbiculare*, or *Malassezia furfur*) or fungistatic.

Terbinafine specifically inhibits the early stages of fungal sterol biosynthesis. This leads to a deficiency in ergosterol and an accumulation of intracellular squalene, resulting in fungal cell death. Terbinafine acts by inhibiting the enzyme squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase does not belong to the cytochrome P450 system. Terbinafine does not affect the metabolism of hormones or other drugs.

Mometasone Furoate is a corticosteroid with marked anti-inflammatory, antipruritic, and antipsoriatic effects. Corticosteroids are steroid hormones secreted by the adrenal glands, along with their synthetic analogs. When used at pharmacological doses, they provide anti-inflammatory effects or suppress immune responses. Topically applied corticosteroids are effective in treating dermatoses responsive to corticosteroids due to their anti-inflammatory and antipruritic properties. In inflammatory and allergic skin conditions, they help prevent inflammation and alleviate symptoms such as itching, burning, or pain.

Topical corticosteroids can be absorbed through normal and damaged skin. The rate of absorption depends on the excipients used in the formulation, the integrity of the epidermis, and the use of occlusive dressings. In inflammatory conditions of the skin, and when the treated area is covered by a dressing, absorption through the skin is increased.

In a croton oil experiment in rats, a single application of Mometasone Furoate was found to be equivalent to Betamethasone Valerate, and after five applications, it was approximately 8 times more effective than Betamethasone Valerate. In a study conducted on guinea pigs, after 14 applications, Mometasone was found to be twice as effective as Betamethasone Valerate in reducing epidermal acanthosis (anti-psoriatic activity) caused by *Malassezia ovalis*.

5.2. Pharmacokinetic Properties

There are no data available on the pharmacokinetic properties of TERBISIL® PLUS after topical application in humans.

Absorption:

Less than 5% of the applied dose of Terbinafine Hydrochloride is absorbed after topical application, resulting in minimal systemic exposure. The systemic absorption of Mometasone Furoate in a 0.1% cream formulation following topical application is very low.

Approximately 0.4% of the applied dose is absorbed through intact skin. After topical application, corticosteroids undergo the same pharmacokinetic processes as systemic corticosteroids, binding to plasma proteins at varying levels. The effects of Mometasone Furoate on the hypothalamic-pituitary-adrenal (HPA) axis have been investigated, and it was found that plasma cortisol levels did not significantly change, consistent with low systemic absorption and bioavailability.

Distribution:

After one week of applying TERBISIL® PLUS, terbinafine concentrations in the affected stratum corneum remained at levels necessary for fungicidal activity for at least 7 days after treatment discontinuation. Since terbinafine levels in the blood are very low after topical application, its metabolism cannot be studied following topical use.

Biotransformation:

After topical application, terbinafine levels in the blood are very low, so its biotransformation cannot be studied. Oral Terbinafine undergoes biotransformation resulting in metabolites that are excreted mainly through urine and have no antifungal activity. No accumulation is expected.

The absorbed Mometasone Furoate is primarily metabolized in the liver.

Elimination:

The elimination half-life of Terbinafine Hydrochloride is 17 hours. After percutaneous absorption, topical corticosteroids are eliminated via the kidneys.

Linearity / Non-linearity:

Since the drug is administered topically, this information is not available.

5.3. Preclinical Safety Data

There are no preclinical safety studies conducted on TERBISIL® PLUS in animal models.

However, genetic toxicity studies conducted with Mometasone Furoate, one of the active ingredients of TERBISIL® PLUS (Ames test, mouse lymphoma assay, and micronucleus test), did not show mutagenic potential.

A series of standard in vitro and in vivo genotoxicity studies with Terbinafine showed no evidence of mutagenic or clastogenic potential. In studies conducted on rats and rabbits, no adverse effects on fertility or other reproductive parameters were observed.

In long-term studies in rats and dogs (up to 1 year), oral doses of up to approximately 100 mg/kg/day of Terbinafine did not show any significant toxic effects. At high oral doses, the liver and possibly the kidneys were identified as potential target organs.

In a two-year oral carcinogenicity study in rats, treatment with Terbinafine at doses of 130 mg/kg/day (male) and 156 mg/kg/day (female) showed no neoplastic or other abnormal findings. At the highest dose level of 69 mg/kg/day, a slight increase in liver tumor formation was observed in male rats. These changes, which were associated with peroxisome proliferation, were considered species-specific and were not observed in other studies with rats, dogs, or monkeys.

In monkeys treated with high oral doses of Terbinafine, retinal refractive disturbances were observed at non-toxic levels (50 mg/kg). These disturbances were related to the presence of a terbinafine metabolite in ocular tissues and resolved after discontinuation of the drug. No histological changes were associated with these disturbances.

6. PHARMACEUTICAL PROPERTIES

6.1 List of Excipients

- Isopropyl Myristate
- Benzyl Alcohol
- Sorbitan Monostearate
- Cetyl Palmitate
- Cetyl Alcohol
- Stearyl Alcohol
- Polysorbate 60
- Hexylene Glycol
- Sodium Hydroxide
- Deionized Water

6.2. Incompatibilities

No known incompatibilities.

6.3. Shelf Life

24 months.

6.4. Special Storage Precautions

Store at room temperature below 25°C. Do not freeze.

6.5. Nature and Contents of Container

The product is available in 20 g and 30 g packaging, in HDPE tubes with white caps, and is presented in a cardboard box with an instruction leaflet.

6.6. Disposal of Unused Medicinal Products and Other Special Precautions

Unused products or waste materials should be disposed of in accordance with the "Regulation on the Control of Medical Waste" and the "Regulation on the Control of Packaging Waste."

7. MARKETING AUTHORIZATION HOLDER

SANTA FARMA ILAC SAN. A.S. H. Edip Adivar / Borucicegi Sokak No: 16 Sisli, Istanbul, Turkey

Tel: (+90 212) 220 64 00

Fax: (+90 212) 222 57 59

8. MARKETING AUTHORIZATION NUMBER

[To be completed nationally]

**9. INITIAL MARKETING AUTHORIZATION DATE / MARKETING
AUTHORIZATION RENEWAL DATE**

[To be completed nationally]

10. PACKAGE LEAFLET RENEWAL DATE

[To be completed nationally]