

SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

TERBISIL® 250 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each tablet contains 281.25 mg terbinafine hydrochloride, equivalent to 250 mg terbinafine

Excipients:

See 6.1 for the list of excipients.

3. PHARMACEUTICAL FORM

Tablet.

White or yellowish-white, round, slightly biconvex tablets. Scored on one side with T25 logo.

4. CLINICAL PARTICULARS

4.2 Therapeutic indications

- Onychomycosis
- Tinea capitis
- Tinea pedis
- Tinea corporis
- Tinea cruris

4.2. Posology and method of administration

Posology/duration and frequency of administration:

The duration of treatment depends on the indication and the severity of the infection.

Unless prescribed otherwise by a doctor:

Children:

No data exists regarding the use in children under 2 years of age (generally bodyweight < 12 kg).

Children with a body weight between 20 and 40 kg	: ½ tablet TERBISIL® (125 mg) once daily
Children weighing > 40 kg	: 1 tablet TERBISIL® (250 mg) once daily

Adults:

TERBISIL® 250 mg tablet, once daily.

Skin infections:

The recommended duration of treatment:

Tinea pedis (interdigital, plantar/moccasin type): 2-6 weeks

Tinea corporis, cruris: 2-4 weeks

Complete resolution of the signs and symptoms infection may not occur until one to two weeks after mycological cure.

In hair and scalp infections:

The recommended duration of treatment:

Tinea capitis: 4 weeks

Tinea capitis is more common in the pediatric age group.

Onychomycosis:

Successful treatment requires a 6 to 12 week period for most of the patients.

Fingernail onychomycosis:

Treatment of 6 weeks duration is generally sufficient in most of the patients.

Toenail onychomycosis:

For most cases, a 12-week treatment is adequate. In patients with slower nail growth a more prolonged treatment course may be needed. Optimum clinical efficacy is reached several months after mycological cure and completion of the treatment, in association with the duration of time required for healthy nail growth.

Method of administration:

The tablets are taken orally with water. Preferably they should be taken on the same hour of the day, irrespective of the meals.

Additional information on special populations

Hepatic impairment

TERBISIL® tablets are not recommended for patients with chronic or active liver disease (see section 4.4. Special warnings and precautions for use).

Renal impairment

The use of TERBISIL® tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 5.2 Pharmacokinetic properties)

Pediatric population: The safety of terbinafine in children has not been definitively demonstrated.

Geriatric population: There is no evidence to suggest that elderly patients (aged 65 years and above) require different dosages or experience different side effects than younger patients. When prescribing TERBISIL® tablets for patients in this age group, the possibility of pre-existing impairment of liver or kidney function should be considered (see section 4.4. Special warnings and precautions for use).

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Liver function

TERBISIL® tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing TERBISIL® tablets, liver function tests should be performed, since hepatotoxicity may occur in patients with and without pre-existing liver disease. Therefore periodic monitoring (after 4-6 weeks of treatment) of liver function tests is recommended. TERBISIL® should be immediately discontinued in case of elevation of liver function tests. Very rare: cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with TERBISIL® tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of TERBISIL® tablets was uncertain (see section 4.8 Undesirable effects). Patients prescribed TERBISIL® tablets should be warned to report immediately any symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine or pale feces. Patients with these symptoms should discontinue taking TERBISIL® treatment.

Dermatological effects

Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms) have been very rarely reported in patients taking TERBISIL® tablets. If progressive skin rash occurs, treatment with TERBISIL® tablets should be discontinued.

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus, as precipitation and exacerbation of psoriasis and cutaneous and systemic lupus erythematosus have been reported in a post-marketing setting.

Hematological effects

Very rare: cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with

TERBISIL® tablets. Etiology of any blood dyscrasias that occur in patients treated with TERBISIL® tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with TERBISIL® tablets.

Renal function

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micro mol/L) the use of TERBISIL® tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties)

Sodium

Terbinafine contains Sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Interactions with other medicines

In vitro and in vivo studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolized by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmic (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed up, especially if the co-administered drug has a narrow therapeutic index (see. Section 4.5 Interactions with other medicinal products).

Other

If deemed retina and ocular changes, pancytopenia, neutropenia, Steven-Johnson syndrome and toxic epidermal necrolysis the treatment should be discontinued.

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

Effect of other medicinal products on terbinafine:

The plasma clearance of terbinafine may be accelerated by drugs, which induce metabolism and may be inhibited by drugs, which inhibit cytochrome P450. Where co-administration of such agents is necessary, the dosage of TERBISIL® tablets may need to be adjusted accordingly.

The following medicinal products may increase the effect or plasma concentration of terbinafine.

Cimetidine decreased the clearance of terbinafine by 33%.

Fluconazole increased the C_{max} and AUC of terbinafine by 52% and 69% respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other drugs which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with terbinafine.

The following medicinal products may decrease the effect or plasma concentration of terbinafine.

Rifampicin increased the clearance of terbinafine by 100%.

Effect of terbinafine on other medicinal products:

Terbinafine may increase the effect or plasma concentration of the following medicinal products:

Caffeine

Terbinafine decreased the clearance of caffeine administered intravenously by 21%

Warfarin:

Terbinafine may increase the effect of warfarin.

Compounds predominantly metabolized by CYP2D6.

In vitro and in vivo studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for compounds predominantly metabolized by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmic (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, especially if they also have a narrow therapeutic window (see section 4.4 Special warnings and precautions for use).

Terbinafine decreased the clearance of desipramine by 82% (see section 4.4. Special warnings and precautions for use).

In studies in healthy subjects characterized as extensive metabolizers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16- to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolizers to poor metabolizers.

Information on other drugs concomitantly used with TERBISIL® resulting in no or negligible interactions

According to the results from studies undertaken in vitro and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance of most drugs that are metabolized via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives) with exception of those metabolized through CYP2D6.

Terbinafine does not interfere with the clearance of antipyrine or digoxin.

There was no effect of terbinafine on the pharmacokinetics of fluconazole. Further there was no clinically relevant interaction between terbinafine and the potential comedications cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual irregularities have been reported in patients taking TERBISIL® tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

Terbinafine may decrease the effect or plasma concentration of the following medicinal products

Terbinafine increased the clearance of cyclosporine by 15%.

Terbinafine may reduce the effect of codeine and tramadol.

Additional information on special populations

No clinical interaction studies have been performed in special populations.

Pediatric populations: No clinical interaction studies have been performed in pediatric populations. The safety of terbinafine in children has not been definitively demonstrated.

4.6. Pregnancy and Lactation

General recommendation

Pregnancy category: B.

Women of child-bearing potential/Birth control (contraception)

Some cases of menstrual irregularities have been reported in patients taking TERBISIL® tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

There are no data to support special recommendations for women of child-bearing potential.

Pregnancy

Data on exposure to terbinafine in pregnant women is limited. Fetal toxicity studies with terbinafine in animals suggest no direct or indirect adverse effects on pregnancy, embryonic/fetal development, childbirth, or post-natal development. TERBISIL® should not be used during pregnancy.

Since documented clinical experience in pregnant women is very limited, TERBISIL® tablets should not be used during pregnancy unless the potential benefits outweigh any potential risks.

Breast-feeding

Terbinafine is excreted in breast milk; mothers receiving oral treatment with terbinafine should therefore not breast-feed.

Fertility

There is no relevant information from human experience. Fertility studies in rats indicated no adverse findings in fertility or reproductive performance.

4.7 Effects on ability to drive and use machines

No studies on the effects of oral Terbinafine treatment on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Adverse reactions

Adverse drug reactions from clinical trials or post-marketing experience are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction 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: ($< 1/10,000$).

Blood and lymphatic system disorders

Uncommon: Anemia

Very rare: Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia.

Immune system disorders

Very rare: Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.

Psychiatric disorders

Common: Depression

Uncommon: Anxiety

Nervous system disorders

Very common: Headache

Common: Dysgeusia* including ageusia*, dizziness.

Uncommon: Paresthesia and hypoesthesia

Eye disorders

Common: Visual impairment

Ear and labyrinth disorders

Uncommon; Tinnitus

Gastrointestinal disorders

Very common: gastrointestinal symptoms (abdominal distension, decreased appetite, dyspepsia, nausea, mild abdominal pain, diarrhea).

Hepatobiliary disorders

Rare: Hepatic failure, hepatitis, jaundice, cholestasis, hepatic enzyme increased

Skin and subcutaneous tissues disorders

Very common: rash, urticaria.

Uncommon: Photosensitivity reaction

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis), erythema multiforme, toxic skin eruption, exfoliative dermatitis, bullous dermatitis.

In patients with progressive rash and erythema, TERBISIL® should be discontinued.

Musculoskeletal and connective tissue disorders

Musculoskeletal and connective tissue disorders

Very common: Musculoskeletal reactions (arthralgia, myalgia).

General disorders

Uncommon: Pyrexia

Common: Fatigue.

Investigations

Uncommon: Weight decreased**

* Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.

** Weight decreased secondary to dysgeusia.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with terbinafine via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders

Anaphylactic reaction, serum sickness-like reaction.

Nervous system disorders

Anosmia including permanent anosmia, hyposmia.

Eye disorders

Vision blurred, visual acuity reduced.

Ear and labyrinth disorders

Hypoacusis, impaired hearing

Vascular disorders

Vasculitis.

Gastrointestinal disorders

Pancreatitis.

Skin and subcutaneous tissue disorders

Drug rash with eosinophilia and systemic symptoms.

Musculoskeletal and connective tissue disorders

Rhabdomyolysis.

General disorders and administration site conditions

Flu-like disease, pyrexia

Investigations

Increased blood creatinine phosphokinase levels.

Reporting of suspected adverse reactions

Post approval reporting of suspected adverse drug reactions is of great importance. Reporting allows continuous monitoring of the drug's benefit/risk balance. Healthcare professionals must report any suspected adverse reaction to Turkish Pharmacovigilance Center (TUFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose and its treatment

A few cases of overdosage (up to 5 g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. The recommended treatment of overdosage consists of eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy, if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group of Terbinafine HCl: Systemic antifungal
ATC Code: D01BA02

Terbinafine is an allylamine which has a broad spectrum of activity against fungal pathogens of the skin, hair and nails including dermatophytes such as Trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. tonsurans, T. violaceum), Microsporum (e.g. M.canis), Epidermophyton floccosum, and yeasts of the genera Candida (e.g. C. albicans) and Pityrosporum. At low concentrations terbinafine is

fungicidal against dermatophytes, moulds and certain dimorphic fungi. Its activity against yeasts is fungicidal 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.

When given orally, the drug concentrates in skin, hair and nails at levels associated with fungicidal activity.

Clinical studies

Onychomycosis

The efficacy of oral terbinafine in the treatment of onychomycosis has been demonstrated in patients with toenail and/or fingernail infections who participated in placebo controlled clinical studies.

Results of the toenail study, as assessed after 36 weeks of follow up (following completion of 12 weeks of treatment), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or >5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).

Results of the fingernail study, as assessed after 18 weeks of follow up (following completion of 6 weeks of treatment), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus clinical cure in 59% of the patients.

The mean time to treatment success for onychomycosis was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing terbinafine therapy, the clinical relapse rate was approximately 15%.

Tinea capitis:

In the three comparative efficacy studies, oral terbinafine (62.5 – 250 mg daily) was given to a total of 117 patients, of whom over 97% were children. Single daily doses were given after the evening meal for 4 weeks (terbinafine) or 8 weeks (griseofulvin). Efficacy, demonstrated by negative mycology tests and a reduction in symptomatology, was evaluated at 8 weeks and at the follow-up examination (Week 12 for two Studies and Week 24 for the third study). Negative mycology test results at follow-up were achieved by 85%, 88% and 72% of patients given terbinafine in the three studies – the corresponding figures for griseofulvin were 73%, 89% and 69%. The treatment was effective (negative mycology plus no, or only mild, symptoms and signs) in 82%, 78% and 69% of terbinafine-treated patients, compared with 66%, 74% and 59% in patients given griseofulvin; the difference was statistically significant in favor of oral terbinafine in the first study.

In a 12 -week randomized, double blind , parallel-group study in patients (> 4 years) with Tinea capitis due to Trichophyton species, the efficacy of 2 and 4 weeks of treatment with oral terbinafine was demonstrated. In a 16 week, randomized, active controlled (open label griseofulvin), parallel group in patients (> 4 years) with Tinea capitis due to Microsporum species, administration of oral terbinafine was based on body weight as follows: <20 kg: 62.5 mg, 20-40 kg: 125 mg, >40 kg: 250 mg, given once

daily. There was no significant difference in complete cure rates between the different treatment duration groups and 6-week treatment showed high complete cure rate (62%) with good tolerability and compliance. In both *Trichophyton* and *Microsporum* studies, oral terbinafine was well tolerated. These results show that terbinafine reduced treatment duration from 6-8 weeks to only 2-4 weeks in *T. capitis* caused by *Trichophyton* species compared to standard therapy with griseofulvin.

In phase II clinical studies conducted in *Tinea capitis*, adverse events reported from the 588 children enrolled were, in general, mild, relatively infrequent and often had an uncertain relationship to treatment. There were 11 reports of elevated SGPT levels and one of taste loss. Other events included mild gastrointestinal or skin symptoms, and laboratory findings indicative of intercurrent infections.

Fungal infections of the skin (*tinea corporis*, *tinea cruris*, *tinea pedis*) and yeast infections of the skin caused by the genus *Candida* (e.g. *Candida albicans*) where oral therapy is generally considered appropriate owing to the site, severity or extent of the infection:

In two placebo controlled studies of 4-week duration and in one active controlled (griseofulvin 250 mg) study of 6 week, terbinafine 250 mg b.i.d showed statistically superior efficacy (negative mycological tests and improvement in clinical symptoms) against placebo and griseofulvin in the treatment of *Tinea corporis/cruris*.

In a double blind, placebo controlled 4 weeks study, oral terbinafine 125 mg b.i.d was compared to placebo in patients with cutaneous candidiasis. 29% of patients in the terbinafine arm and 17% of patients on placebo demonstrated mycological cure at the end of treatment and 67% of terbinafine treated patients had negative mycological results at the end of follow up. Given the above response rates, 2 weeks therapy of terbinafine should be the minimum duration of treatment period and approximately half of the patients would require 3-4 weeks of treatment to achieve cure.

Two double blind, controlled studies compared terbinafine 125mg b.i.d. to placebo and to griseofulvin 250mg b.i.d. in the treatment of *Tinea pedis*. 65% of patients on terbinafine reported mycological cure at follow up whereas none of the placebo treated patients responded.

In the other study, terbinafine was shown to be significantly more effective than griseofulvin at follow up after 6 weeks therapy (45% and 38%, respectively). When observed after 10 months, the cure rate in terbinafine and griseofulvin patients were 94% and 30%, respectively.

5.2. Pharmacokinetic properties

Absorption

Following oral administration, terbinafine is well absorbed (>70%). A single oral dose of 250 mg terbinafine resulted in a mean peak plasma concentration of 1,3 microgram/mL within 1,5 hours of administration. At steady-state (70% steady state is achieved in approximately 28 days), in comparison to a single dose, peak concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2,3.

Terbinafine bioavailability is moderately affected by food intake (a less than 20% increase in AUC); however this increase does not necessitate any dose adjustments.

Distribution:

Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and accumulates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skin. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks after commencing therapy.

Biotransformation:

Terbinafine is metabolized rapidly and extensively by at least seven CYP isoenzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity.

Elimination:

The metabolites are excreted predominantly in the urine. From the increase in plasma AUC at steady state an effective half-life of ~30 hours was calculated. Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16,5 days.

Bioavailability:

The absolute bioavailability of terbinafine from terbinafine tablets as a result of first-pass metabolism is approximately 50%.

Special populations

Geriatric patients:

No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been observed.

Pediatric patients:

The safety in children has not been definitively established.

Oral terbinafine was well tolerated in children over 2 years of age.

Renal - Hepatic Failure

The elimination rate may be reduced in patients with renal or hepatic impairment resulting in higher blood levels of Terbinafine

Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance <50 mL/min) or with pre-existing liver disease have shown that the clearance of terbinafine tablets may be reduced by about 50%.

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, an increased incidence of liver tumors was observed in males at the highest dose level of 69 mg/kg a day. 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 high-dose studies in monkeys, refractive irregularities were observed in the retina at the higher doses (non-toxic effect level 50 mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after drug discontinuation.

An 8-week oral study in juvenile rats provided a no-toxic-effect level (NTEL) of close to 100 mg/kg/day, with the only finding being slightly increased liver weights, while in maturing dogs at ≥ 100 mg/kg/day (AUC values about 13x (m) and 6x (f) those in children), signs of central nervous system (CNS) disturbance including single episodes of convulsions in individual animals were observed.

Similar findings have been observed at high systemic exposure upon intravenous administration of terbinafine to adult rats or monkeys.

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

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

6. PHARMACEUTICAL CHARACTERISTICS

6.1. List of excipients

Colloidal silicone dioxide
Magnesium stearate
Hydroxypropyl methyl cellulose
Microcrystalline cellulose
Sodium starch glycolate

6.2. Incompatibilities

None.

6.3. Shelf life

48 months.

6.4 Special precautions for storage

Store in its original packing at room temperature below 30°C and protect from light.

6.5. Nature and contents of container

Blister packs of 14 and 28 tablets.

6.6. The disposal of medicinal waste and other special precautions.

The unused products or medical waste should be disposed of in accordance with the “Directives for the Control of Medicinal Waste” and with the “Directive for Packing and Packing Waste”.

7. AUTHORIZATION HOLDER

Halide Edip Adivar mahallesi / Boru Çicegi Sokak No: 16 Sisli, Istanbul, Turkey Tel: 0212 220 64 00
Fax: 0212 222 57 59

8. AUTHORIZATION NUMBER

197/83

9. DATE OF INITIAL AUTHORIZATION/RENEWAL OF AUTHORIZATION

Initial license date: 23.08.2001

Date of authorization renewal: 23.08.2001

10. DATE OF RENEWAL OF SmPC

23.08.2001