

Summary of main Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

TERBINOL® 250

Terbinafine hydrochloride

1.1. **Strength** 250 mg

1.2. **Pharmaceutical form** Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg terbinafine (as terbinafine hydrochloride).

Excipients with known effect : none

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

White, round, one face notched tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of fungal infections of the skin and nails caused by dermatophytes, such as Trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum: Tinea corporis, Tinea cruris and Tinea pedis.
- Treatment of fungal infections of the nails: onychomycosis caused by dermatophytes.

4.2. Posology and mode of administration

4.2.1. Posology

- **Adults and children > 12 years old**
1 tablet of 250 mg once daily.

The duration of treatment varies according to the indication and the severity of the infection:

- Skin infections (Tinea pedis, interdigital, plantar/moccasin type): 2 to 6 weeks. Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.
- Tinea corporis: 4 weeks.

- Tine cruris : 2 to 4 weeks
- Onychomycosis: the general duration of treatment is between 6 weeks and 3 months.
 - Fingernails: in general 6 weeks.
 - Toenails: in general 12 weeks, some patients need treatment up till 6 months.

Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure and is only seen several months after stopping treatment, which is the time for growth of a healthy nail.

4.2.2. Special populations

Liver impairment

Terbinol tablets are contraindicated for patients with chronic or active hepatic disease (see sections 4.3 and 4.4).

Renal impairment

The use of Terbinol tablets has not been adequately studied in patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micro mol/L) and is therefore not recommended in this population.

Geriatric population

There is no evidence to suggest that elderly patients require different dosages or experience side-effects different to those of younger patients. The possibility of impairment of liver or kidney function should be considered in this age group.

4.2.3. Paediatric population

- For children < 2 years (weight mostly < 12 kg): no data are available.
- *Children > 2 years*
For children < 20 kg: Terbinol tablets are not recommended, because the tablets cannot be divided in 4 to obtain a dosage of 62,5 mg.
For children with a body weight between 20 to 40 kg: 125 mg (= one half tablet, once daily).

4.2.4. Method of administration

The tablets are taken orally with water. They should preferably be taken at the same time each day and can be taken on an empty stomach or after a meal.

4.3. Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Chronic or active hepatic disease
- Severe renal impairment: creatinine clearance less than 30 mL/min

4.4. Special warning and precautions for use

4.4.1. General information

Patients prescribed Terbinol tablets should be instructed to report immediately any signs or symptoms suggestive of liver dysfunction such as pruritus, unexplained persistent nausea, decreased appetite, anorexia, jaundice, vomiting, fatigue, right upper abdominal pain, dark urine, or pale stools. Patients with these symptoms should discontinue taking oral terbinafine and the patient's liver function should be immediately evaluated.

Hepatic Function

Terbinol tablets are contraindicated for patients with chronic or active hepatic disease. Before prescribing Terbinol tablets, a liver function test should be performed and any pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease. Therefore periodic monitoring (after 4-6 weeks of treatment) of liver function test is recommended.

Terbinol tablets should be immediately discontinued in case of elevation of liver function test.

Very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with orally administered terbinafine. In the majority of liver failure cases the patients had serious underlying systemic conditions.

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 terbinafine. If progressive skin rash occurs, treatment with Terbinol tablets should be discontinued.

Terbinol should be used with caution in patients with pre-existing psoriasis, as very rare cases of exacerbation of psoriasis have been reported.

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Dermatological and mucosal infections (Candida, pityriasis versicolor)

Orally administered terbinafine is not effective or not effective enough against skin infections by *Candida* spp. or *Pityrosporon ovale* (pityriasis versicolor), and neither against mucosal infection due to *Candida* spp. (including vaginal candidose).

Haematological effects

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients orally treated with terbinafine. Aetiology of any blood dyscrasias that occur in patients orally treated with terbinafine should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Terbinol tablets. The patient's blood formula should be regularly evaluated.

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 orally administered terbinafine has not been adequately studied, and therefore, is not recommended.

4.4.2. Pediatric population

See 4.4.1.

4.5. Interactions with other medicinal products and other forms of interactions

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 Terbinol tablets may need to be adjusted accordingly.

- The following medicinal products may **increase the effect** or plasma concentration of terbinafine:

- Cimetidine
- Fluconazole
- Ketoconazole
- Amiodarone
- The following medicinal products may **decrease the effect** or plasma concentration of terbinafine:
 - Rifampicin

Effect of terbinafine on other medicinal products

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

Terbinafine does not interfere with the pharmacokinetic parameters of fluconazole. In addition, based on drug interaction studies in 18 subjects per study, no clinically relevant interactions were observed between terbinafine and concomitantly co-administered medicinal products, namely cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine and theophylline.

Some cases of irregular menstruation have been reported in patients taking orally terbinafine concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

- Terbinafine may **increase the effect** or plasma concentration of the following medicinal products:
 - Caffeine
 - Compounds predominantly metabolised by CYP2D6: tricyclic antidepressants (TCA's), β -blockers, selective serotonin reuptake inhibitors (SSRIs), anti-arrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, Terbinafine is a potent inhibitor of the isoenzyme CYP2D6, which should be considered if Terbinol tablets are combined with medicinal products metabolised by this isoenzyme. These patients should be followed up, especially when these drugs have a narrow therapeutic index.
 - Desipramine

- Dextromethorphan
- Terbinafine may **decrease the effect** or plasma concentration of the following medicinal products:
 - Ciclosporin

Interactions with food / drinks

The bioavailability of terbinafine is poorly influenced by simultaneous intake of food and drinks, but not enough to adjust the dose: influence on AUC increase less than 20%.

4.6. Pregnancy, , lactation and fertility

4.6.1. Fertility

Foetal toxicity and fertility studies in animals suggest no adverse effect.

4.6.2. Pregnancy

Foetal toxicity and fertility studies in animals suggest no adverse effects. Since clinical experience in pregnant women is very limited, Terbinol tablets should not be used during pregnancy unless clinical condition of the woman requires treatment with oral terbinafine and the potential benefit for the mother outweighs the potential risks for the foetus..

4.6.3. Lactation

Terbinafine is excreted in breast milk. Therefore, Terbinol tablets should not be used during the period of breastfeeding.

4.7. Effects on the ability to drive and use machines

No studies on the effects of orally administered terbinafine 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. Undesirable effects

The frequencies of adverse reactions reported with terbinafine are defined as:

- 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)

Blood and lymphatic system disorders	
Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia	Very rare
Anaemia.	Not known
Immune system disorders	
Anaphylactic reaction, angioedema, cutaneous and systemic lupus erythematosus	Very rare
Anaphylactic reactions, serum sickness-like reaction	Not known
Metabolism and nutrition disorders	
Decreased appetite	Very common
Psychiatric disorders	
Anxiety, depression	Not known
Nervous system disorders	
Headache	Common
Hypogeusia, ageusia	Uncommon
Dizziness, paraesthesia and hypoaesthesia	Rare
Anosmia	Not known
Eye disorders	
Visual impairment, blurred vision, visual acuity reduced	Not known
Ear and labyrinth disorders	
Vertigo	Very rare
Hypoacusis, hearing impaired, tinnitus	Not known
Vascular disorders	
Vasculitis	Not known
Gastrointestinal disorders	
Abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea	Very common
Pancreatitis	Not known
Hepatobiliary disorders	
Hepatic failure, hepatic enzymes increased	Rare
Hepatitis, jaundice, cholestasis	Rare
Skin and subcutaneous tissue disorders	
Rash, urticaria	Very common

Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthemous pustulosis (AGEP), psoriasiform eruptions or exacerbation of psoriasis, alopecia	Very rare
Drug rash with eosinophilia and systemic symptoms (DRESS)	Not known
Photosensitivity reaction, photodermatitis, photosensitivity allergic reaction and polymorphic light eruption	Not known
Musculoskeletal and connective tissue disorders	
Arthralgia, myalgia	Very common
Rhabdomyolysis	Not known
General disorders and administration site conditions	
Malaise	rare
Fatigue	Very rare
Influenza like illness, pyrexia	Not known
Investigations	
Weight decrease secondary to dysgeusia	Uncommon
Blood creatinine phosphokinase increased, weight decreased	Not known

4.9. Overdose

A few cases of overdose (up to 5 g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. Recommended treatment for overdose consists of eliminating the active substance, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: Antifungal for systemic use -ATC Code: D01BA02.

Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations orally administered terbinafine is fungicidal against dermatophytes (*Trichophyton* spp, *Microsporum* spp, *Epidermophyton floccosum*), moulds (*Aspergillus* spp, *Scopulariopsis brevicaulis*) and certain dimorphic fungi (*Sporothrix schenckii*). The activity versus yeasts (*Candida parapsilosis*) is fungicidal or fungistatic depending on the species. This fungicidal effect is due to intracellular squalene accumulation and ergosterol deficiency, which induce cell death of the fungus. Terbinafine interferes at an early stage of fungal sterol biosynthesis, an essential component of the fungus cell membrane, and specifically inhibits squalene epoxidase in the cell membrane of the fungus. This enzyme is not linked to the cytochrome P450 system. Therefore, terbinafine does not influence the metabolism of hormones or other drugs.

After an oral dose, terbinafine accumulates at fungicidal concentrations in the skin, hair, body hair and nails. It is still present 15 to 20 days after stopping treatment.

5.2. Pharmacokinetic properties

Absorption

- Terbinafine following oral administration is well-absorbed.
- The peak plasma concentration is reached within 2 hours after oral administration of a single dose of 250 mg terbinafine.
- In an "equilibrium" state (70% of steady state is reached after about 28 days), the plasma peak of terbinafine, compared with a single dose, was 25% higher on average and plasma AUC increased by a factor of 2.3 when compared to single dose administration.

Distribution

Terbinafine binds strongly to plasma proteins (99%). It diffuses rapidly through the dermis and accumulates in the lipophilic horny layer. Terbinafine is also excreted in sebum, high concentrations are observed in hair follicles, hair and skin areas rich in

sebum. It has also been shown that terbinafine is present in the nails during the first weeks of treatment.

Biotransformation / Metabolism

Terbinafine is rapidly and extensively metabolized by 7 CYP-like isoenzymes, mainly CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation produces metabolites without antifungal activity, which are mainly excreted by the urinary tract.

Elimination

Liver first pass effect around 40%.

Excretion mainly via the urinary tract.

Special populations

Terbinafine plasma concentrations are **not influenced by age**, but the rate of elimination may be reduced in patients with impaired hepatic or renal function, resulting in increased plasma concentrations of terbinafine. In patients with **pre-existing mild-to-severe hepatic impairment**, single-dose pharmacokinetic studies have demonstrated that the clearance of terbinafine can be reduced by approximately 50%.

5.3. Preclinical safety data

The approximate LD50 value of orally administered terbinafine is over 4 g/kg in both mice and rats.

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 100mg/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 tumours was observed in males at the highest dosage level of 69 mg/kg, at which systemic exposure was similar to clinical exposure. The mechanism of tumour development has not been established. The clinical relevance is unknown. 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, dogs or monkeys.

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

An 8-week oral study conducted in juvenile rats determined a non-toxic effect level (NTEL) of almost 100 mg / kg / day, the only finding being a slight increase in body weight. Whereas in adult dogs receiving ≥ 100 mg / kg / day (AUC values equal to approximately 13x (m) and 6x (f) those observed in children), there were signs of central nervous system, including some episodes of convulsions in individual animals. The same results were observed with high systemic exposure following intravenous administration of terbinafine to rats or adult monkeys.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Hypromellose,
- Croscarmellose sodium,
- Microcrystalline cellulose ,
- Colloidal silica,
- Magnesium stearate,

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months (2 years)

6.4. Special precautions for storage

Store below 30 ° C in the original package.

6.5. Nature and contents of container

The tablets are packaged in a blister pack with 14 tablets.

Box with 14 tablets .

6.6. Special precautions for disposal and other handlings

No special requirements for disposal.

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

7- MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS**7.1 Marketing Authorisation Holder**

Dafra Pharma GmbH,
Mühlenberg 7, 4052 Basel, Switzerland.

7.2 Manufacturer

Nobel Ilaç, San. Ve. Tic. A.S., Sancaklar 81100 Düzce, Turkey.

8- MARKETING AUHORISATION NUMBER

See list of MAs per country

9- DATE OF FIRST REGISTRATION

See list of MAs per country

10- DATE OF REVISION OF TEXT

01/2021