Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Terbinol

Terbinafine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 281.25 mg terbinafinehydrochloride equivalent to 250 mg terbinafine.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White, round, one face notched tablets.

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 (see Section 4.4), where oral therapy is considered appropriate due to the site, severity or extent of the infection.
- Treatment of fungal infections of the nails: onychomycosis caused bydermatophytes.

4.2. Posology and mode of administration

4.2.1. Posology

- **Adults and children > 12 years old**

  1 tablet of 250 mg, once daily.

- **Paediatric population**

  Children < 2 years

  For children < 2 years (weight mostly < 12 kg): no data are available.

  Children > 2 years

  - For children < 20 kg: Terbinol Tablets is 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.

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

1. Skin infections (Tinea pedis (interdigital, plantar/moccasin type), Tinea corporis,

Tinea cruris): 2 to 6 weeks.Complete resolution of the signs and symptoms of infection may notoccur until several weeks after mycological cure.

2. Tinea capitis: 4 weeks.
3. Onychomycosis:

a. Toenails: up till 12 weeks.

b. Fingernails: 6 to 16 weeks.

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

i. Special populations

Liver impairment

Terbinol Tablets are contraindicated for patients with chronic or active hepaticdisease (see sections 4.3 Contraindications and 4.4 Special warnings and precautions for use).

Renal impairment

The use of Terbinafine containing tablets has not been adequately studied in patients withrenal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micro mol/L) and is therefore not recommendedin this population (see section 4.4 Special warnings and precautions for use).

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 inthis age group (see section 4.4 Special warnings and precautions for use).

ii. Paediatric population

Oral use of terbinafine is well tolerated in children of > 2 years.

iii. Method of administration

The scored 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 orafter a meal

4.3. Contraindications

-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

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 (pytiriasis versicolor), and neither against mucosal infection due to Candida spp. (including vaginal candidose).

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 preexisting 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, orrequiring 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 (see sections 4.3 Contraindications and 4.8Undesirable effects).

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 beimmediately evaluated.

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, Terbinol Tablets shouldbe discontinued.

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

Haematological effects

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients orally treated withterbinafine. 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 withTerbinol 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(see section 5.2 Pharmacokinetic properties).

Inhibitor of CYP2D6

Terbinafine is a potent inhibitor of the isoenzyme CYP2D6, which should be considered if Terbinol Tablets are combined with medicinal products metabolised bythis isoenzyme, such as tricyclic antidepressants, β-blockers, selective serotonin reuptake inhibitors (SSRIs), anti-arrhythmics (including classes 1A, 1B and 1C) andmonoamine oxidase inhibitors (MAOIs) type B. These patients should be followedup, especially when these drugs have a narrow therapeutic index (see section 4.5"Interaction with other medicinal products and other forms of interaction"). Dose adjustments may be necessary.

Immunocompromised patients

The patient's blood formula should be regularly evaluated if treated for more than 6 weeks.

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 mayneed to be adjusted accordingly.

- *The following medicinal products may increase the effect or plasmaconcentration of terbinafine:*
  - **Cimetidine** decreased the clearance of terbinafine by 33%.
  - **Fluconazole** increased the Cmax 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 plasmaconcentration of terbinafine:*
  - **Rifampicin** increased the clearance of terbinafine by 100%.

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 enhancingthe 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 (see below).

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

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:** Terbinafine decreased the clearance of caffeine administered intravenously by 19%.
  - **Compounds predominantly metabolised 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 patients receiving

    compounds predominantly metabolised by CYP2D6, e.g. certain members of the following drug classes, **tricyclic antidepressants (TCA's), β-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (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).
  - **Atenolol** is predominantly eliminated in unchanged form; therefore, terbinafine has no influence on atenolol.
  - Terbinafine decreased the clearance of **desipramine** by 82%.
  - 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 (genotype) to poor metabolizer status (phenotype).

- Terbinafine may decrease the effect or plasma concentration of the following medicinal products:
  - **Ciclosporin**: Terbinafine increased the clearance of ciclosporin by 15%.

Interactions with food / drinks

The bioavailability of terbinafine is poorly influenced (AUC increase less than 20%), but not

enough to adjust the dose.

4.6. Fertility, pregnancy and lactation

4.6.1. Fertility

There are no relevant data on fertility in humans. Fertility studies in animals do not suggest any toxic effects.

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 benefits for the mother outweigh any potential risks for the foetus.

4.6.3. Lactation

Terbinafine and metabolites were found in neonates / infants breastfed by treated women. The effect of terbinafine on new-borns / infants is unknown.Terbinol tablets should not be used while 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

Side effects are generally mild to moderate, and transient. The following adverse reactions have been observed in the clinical trials or during post-marketing experience with terbinafine medicinal products.

Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, <1/100); Rare (1/10,000, < 1/1,000); Very rare (< 1/10,000), Not known(frequency cannot be estimated from available data).

Blood and lymphatic system disorders	
Neutropenia, agranulocytosis, thrombocytopenia,pancytopenia	Very rare
Anaemia.	Uncommon
Immune system disorders	
Anaphylactoid reaction, angioedema, cutaneous and systemiclupus erythematosus	Very rare
Anaphylactic reactions, serum sickness-like reaction	Not known
Metabolism and nutrition disorders	
Decreased appetite	Very common

Psychiatric disorders	
Depression	Common
Anxiety	Uncommon
Anxiety , depression secondary to dysgeusia	Not known
Nervous system disorders	
Headache	Very common
Hypogeusia[1], ageusia[1]	Common
Dizziness	Common
Paraesthesia and hypoaesthesia	Uncommon
Anosmia	Not known
Eye disorders	
Visual impairment	Common
Blurred vision, visual acuity reduced	Not knonw
Ear and labyrinth disorders	
Tinnitus	Common
Hypoacusis, hearing impaired,	Not known
Vascular disorders	
Vasculitis	Not known

Gastrointestinal disorders	
Abdominal distension, dyspepsia, nausea, abdominal pain,diarrhea	Very common
Pancreatitis	Not known
Hepatobiliary disorders	
Hepatic failure, hepatitis, jaundice, cholestasis hepatic enzymes increased (see section 4.4)	Rare
Skin and subcutaneous tissue disorders	
Rash, urticaria	Very common
Photosensitivity reaction, photodermatosis, photosensitivity allergic reaction and polymorphic light eruption	Uncommon
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
Musculoskeletal and connective tissue disorders	
Arthralgia, myalgia	Very common

Rhabdomyolysis	Not known
General disorders and administration site conditions	
Fatigue	Common
Influenza like illness, pyrexia	Not known
Investigations	
Blood creatinine phosphokinase increased, weight decreased[2]	Not known

1. Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.
2. Weight decreased secondary to hypogeusia.

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:

Oral antifungal agent, 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 schenkii). The activity versus yeasts (Candida parapsilosis) is fungicidal or fungistaticdepending 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 earlystage of fungal sterol biosynthesis, an essential component of the fungus cell membrane, and specifically inhibits squalene epoxidase in the cell membrane of thefungus. 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 (>70%).

The Cmax of 0.97 μg / ml is reached within 2 hours after oral administration of a single dose of 250 mg terbinafine.
The half-life of absorption is 0.8 hours, and the half-life of distribution is 4.6 hours.Although food intake slightly influences the bioavailability of terbinafine, it is not necessary to adjust the dose.
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 averageand Plasma ASF increased by a factor of 2.3.

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.

Elimination
Biotransformation produces metabolites without antifungal activity, which are mainly excreted by the urinary tract. The elimination half-life is 17 hours.
No accumulation of the product was found in the plasma.

Special populations

Paediatric and geriatric population
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.

Patients with liver disorders
In patients with pre-existing mild-to-severe hepatic impairment, single-dose pharmacokinetic studies have demonstrated that the clearance of terbinafine can bereduced by approximately 50%.

5.3. Preclinical safety data

The approximate LD50 value of orally administered terbinafine is over 4 g/kg in bothmice 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 abnormalfindings 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 dosage level of 69 mg/kg, at whichsystemic exposure was similar to clinical exposure. The mechanism of tumor 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 wereassociated with the presence of a terbinafine metabolite in ocular tissue and disappeared after discontinuation of the active substance. They were not associatedwith 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 followingintravenous 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 observedin 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.

6.4. Special precautions for storage

Store below 30 ° C in the original package to protect from light.

6.5. Nature and contents of container

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

The blisters are packaged in a cardboard box with one blister per box.

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 withlocal requirements.

7- MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1 Marketing Authorization 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

Rwanda FDA-HMP-MA-0069

9- DATE OF FIRST REGISTRATION

First Authorization: 01 June 2021

10- DATE OF REVISION OF TEXT

April 2022