SUMMARY PRODUCT CHARACTERISTICS

Name of the Medicinal Product:

ONCOSIL-250 (Terbinafine Tablets USP 250 mg)

1. Qualitative and Quantitative Composition:

Each uncoated tablet contains:

Terbinafine Hydrochloride USP

Equivalent to Terbinafine: 250 mg

Excipients: q.s.

For a full list of Excipients see section 6.1

2. Pharmaceutical Form

Tablet

Off White, oblong, uncoated tablets having a break line on one side and plain on other side.

3. Clinical Particulars

3.1 Therapeutic indications:

ONCOSIL – 250 is indiacted for fungal infections of the skin and nails caused by Trichophyton (eg. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum.

ONCOSIL - 250 is indicated in the treatment of ringworm (tinea corporis, tinea cruris and tinea pedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection and also in the treatment of onychomycosis.

3.2 Posology and method of administration:

Adults

250mg once daily

The duration of treatment varies accordingly to the infection and the severity of the infection.

Skin infections

Likely duration of treatment are as follows:

Tinea Pedis (interdigital, planar/moccasin type): 2 to 6 weeks

Tinea corporis: 4 weeks

Tinea cruris: 2 to 4 weeks

Onychomycosis

The duration of treatment for most patients is between 6 weeks and 3 months. Treatment Period of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of the big toe, or patients of younger age. In the treatment of toenail infections, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer. Poor nail outgrowth during the first week of treatment may enable identification of those patients in whom longer therapy is required.

Recommended route of administration: oral use

weeks, the diagnosis should be verified by a physician.

Method of administration: For oral administration.

3.3 Contraindications

There is no other contraindication except Hypersensitivity to Terbinafine Hydrochloride.

3.4 Special warning and precautions for use:

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. ONCOSIL - 250 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 ONCOSIL - 250. In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of ONCOSIL - 250 was uncertain. Patients prescribed ONCOSIL - 250 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.

3.5 Interaction with other medicinal products and other forms of Interactions

Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including Torsade de Pointes in patients to whom Terbinafine Hydrochloride and cisapride were coadministered. A controlled study found that concomitant Terbinafine Hydrochloride 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QT interval. Concomitant treatment with Terbinafine Hydrochloride and cisapride is contraindicated.

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of Terbinafine Hydrochloride failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of Terbinafine Hydrochloride demonstrated that Terbinafine Hydrochloride taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of Terbinafine Hydrochloride at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration of Terbinafine Hydrochloride at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of Terbinafine Hydrochloride with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsade depointes*. Coadministration of Terbinafine Hydrochloride and astemizole is contraindicated.

Pimozide: Although not studied in vitro or in vivo, concomitant administration of Terbinafine Hydrochloride with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of Terbinafine Hydrochloride and pimozide is contraindicated.

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of Terbinafine Hydrochloride with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of*torsades de pointes*. Coadministration of Terbinafine Hydrochloride and quinidine is contraindicated.

Erythromycin: Concomitant use of Terbinafine Hydrochloride and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, Torsades de Pointes)

and consequently sudden heart death. Coadministration of Terbinafine Hydrochloride and erythromycin is contraindicated.

Concomitant use of the following other medicinal products cannot be recommended:

Halofantrine: Terbinafine Hydrochloride can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of Terbinafine Hydrochloride and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided.

Concomitant use of the following other medicinal products lead to precautions and dose adjustments: The effect of other medicinal products on Terbinafine Hydrochloride

Rifampicin: Concomitant administration of Terbinafine Hydrochloride capsule and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life of Terbinafine Hydrochloride. In patients receiving concomitant rifampicin, an increase in the Terbinafine Hydrochloride capsule dose should be considered. Interaction studies have shown that when oral Terbinafine Hydrochloride is coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of Terbinafine Hydrochloride absorption occurs.

The effect of Terbinafine Hydrochloride on other medicinal products

Terbinafine Hydrochloride: is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Terbinafine Hydrochloride is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compoundsmetabolized by CYP2C9 and CYP3A4 coadministered with Terbinafine Hydrochloride. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of Terbinafine Hydrochloride persists 4-5 days after discontinuation of Terbinafine Hydrochloride treatment due to the long half-life of Terbinafine Hydrochloride.

Alfentanil: During concomitant treatment with Terbinafine Hydrochloride (400 mg) and intravenous alfentanil (20 μg/kg) in healthy volunteers the alfentanil AUC 10 increased 2-fold, probably through inhibition of CYP3A4.Dose adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline: Terbinafine Hydrochloride increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at

initiation of the combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary

Amphotericin B: Concurrent administration of Terbinafine Hydrochloride and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving Terbinafine Hydrochloride concurrently with warfarin. During concomitant treatment with Terbinafine Hydrochloride and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type anticoagulants concurrently with Terbinafine Hydrochloride the prothrombin time should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, Terbinafine Hydrochloride resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of Terbinafine Hydrochloride 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Terbinafine Hydrochloride 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and halflife 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with Terbinafine Hydrochloride. If concomitant benzodiazepine therapy is necessary in patients being treated with Terbinafine Hydrochloride, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Terbinafine Hydrochloride inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect. Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. Terbinafine Hydrochloride has the potential to increase the

systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended. Celecoxib: During concomitant treatment with Terbinafine Hydrochloride (200 mg daily) and celecoxib (200 mg) the celecoxib Cmax and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with Terbinafine Hydrochloride.

Cyclophosphamide: Combination therapy with cyclophosphamide and Terbinafine Hydrochloride results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl Terbinafine Hydrochloride interaction was reported. Furthermore, it was shown in healthy volunteers that Terbinafine Hydrochloride delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when Terbinafine Hydrochloride is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Immunosuppresors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Terbinafine Hydrochloride significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with Terbinafine Hydrochloride 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, Terbinafine Hydrochloride may increase serum concentrations of everolimus through inhibition of CYP3A4. Sirolimus: Terbinafine Hydrochloride increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination

may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

Tacrolimus: Terbinafine Hydrochloride may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Losartan: Terbinafine Hydrochloride inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin Il-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone: Terbinafine Hydrochloride may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The Cmax and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with Terbinafine Hydrochloride compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when Terbinafine Hydrochloride was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.Although not specifically studied, Terbinafine Hydrochloride has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Terbinafine Hydrochloride inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg Terbinafine Hydrochloride and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC24 by 75% and Cmin by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with Terbinafine Hydrochloride was discontinued. The discontinuation of Terbinafine Hydrochloride presumably caused an enhanced CYP3A4 activity which led to increased

metabolism of prednisone. Patients on long-term treatment with Terbinafine Hydrochloride and prednisone should be carefully monitored for adrenal cortex= insufficiency when Terbinafine Hydrochloride is discontinued. Rifabutin: Terbinafine Hydrochloride increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom Terbinafine Hydrochloride and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Terbinafine Hydrochloride increases the AUC and Cmax of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

Sulfonylureas: Terbinafine Hydrochloride has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.

Theophylline: In a placebo-controlled interaction study, the administration of Terbinafine Hydrochloride 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving Terbinafine Hydrochloride. Therapy should be modified if signs of toxicity develop. Vinca alkaloids: Although not studied, Terbinafine Hydrochloride may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and Terbinafine Hydrochloride, CNS related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of Terbinafine Hydrochloride treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral Terbinafine Hydrochloride (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy malesubjects

resulted in an increase in Cmax and AUCτ of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and Terbinafine Hydrochloride that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after Terbinafine Hydrochloride.

Zidovudine: Terbinafine Hydrochloride increases Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with Terbinafine Hydrochloride. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of Terbinafine Hydrochloride as well as the effects of Terbinafine Hydrochloride on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between Terbinafine Hydrochloride and azithromycin.

Oral contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of Terbinafine Hydrochloride. There were no relevant effects on hormone level in the 50 mg Terbinafine Hydrochloride study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of Terbinafine Hydrochloride at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

3.6 Fertility, Pregnancy and Lactation:

Pregnancy: Data from several hundred pregnant women treated with standard doses (<200 mg/day) of Terbinafine Hydrochloride, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400- 800 mg daily) of Terbinafine Hydrochloride for coccidioidomycosis. The relationship between Terbinafine Hydrochloride

use and these events is unclear. Studies in animals have shown reproductive toxicity. Terbinafine Hydrochloride in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary. Terbinafine Hydrochloride in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding: Terbinafine Hydrochloride passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg Terbinafine Hydrochloride or less. Breast-feeding is not recommended after repeated use or after high dose Terbinafine Hydrochloride.

Fertility: Terbinafine Hydrochloride did not affect the fertility of male or female rats.

3.7 Effects on ability to drive and use machines.

Patients should be warned about the potential for dizziness or seizures while taking Terbinafine Hydrochloride tablets and should be advised not to drive or operate machines if any of these symptoms occur.

3.8 Side Effects:

Common or very Common: Skin reaction, Appetite decreased, arthralgia, diarrhoea, gastrointestinal discomfort, gastrointestinal disorder, headache, myalgia, nausea.
Uncommon: With oral use Taste altered
Rare or very rare: Agranulocytosis, alopecia, cutaneous lupus erythematosus, dizziness, hepatic disorder, malaise, neutropenia, photosensitivity reaction, sensational abnormal, severe cutaneous adverse reactions, systemic lupus erythematosus, thrombocytopenia, vertigo
In case of accidental contact with the eyes, terbinafine hydrochloride may be irritating to the eyes.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Agents.

3.9 OVERDOSAGE

The low systemic absorption of topical terbinafine renders overdosage extremely unlikely.

4. Pharmacological Properties:

4.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Antifungals for systemic use .

ATC code: D01BA02

Mode of action

Terbinafine Hydrochloride is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylations, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of Terbinafine Hydrochloride. Terbinafine Hydrochloride has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems. Terbinafine Hydrochloride 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of childbearing age. Terbinafine Hydrochloride 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single multiple doses of Terbinafine Hydrochloride 50 mg do not affect its metabolism.

PK/PD relationship: In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida*spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of Terbinafine Hydrochloride. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly, cure is less likely for infections caused by strains with a higher Terbinafine Hydrochloride MIC.

Susceptibility *in vitro*

I*n vitro*, Terbinafine Hydrochloride displays antifungal activity against most clinically common *Candida* species (including *C. albicans, C. parapsilosis, C. tropicalis). C. glabrata* shows a wide range of susceptibility while *C. krusei* is resistant to Terbinafine Hydrochloride. Terbinafine Hydrochloride also exhibits activity *in vitro* against *Cryptococcus neoformans* and *Cryptococcus. gattii* as well as the endemic moulds *Blastomyces dermatiditis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

Mechanism(s) of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to Terbinafine Hydrochloride which impacts adversely efficacy *in vivo* and clinically. There have been reports of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to Terbinafine Hydrochloride (e.g. *Candida krusei*). Such cases may require alternative antifungal therapy.

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for Terbinafine Hydrochloride for *Candida* species (EUCAST Terbinafine Hydrochloride rational document (2007)-version 2). These have been divided into nonspecies related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S<R/>)					Non-species related breakpointsAS<R/>
	Candida albicans	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*	*Candida tropicalis*	
Terbinafine Hydrochloride	2/4	IE	--	2/4	2/4	2/4

A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

IE = There is insufficient evidence that the species in question is a good target for therapy with the medicinal product

4.2 Pharmacokinetic interactions

Pharmacokinetic Properties

The pharmacokinetic properties of Terbinafine Hydrochloride are similar following administration by the intravenous or oral route.

Absorption: After oral administration Terbinafine Hydrochloride is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.

Distribution: The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%). Terbinafine Hydrochloride achieves good penetration in all body fluids studied. The levels of Terbinafine Hydrochloride in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, Terbinafine Hydrochloride levels in the CSF are approximately 80% the corresponding plasma levels. High skin concentration of Terbinafine Hydrochloride, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Terbinafine Hydrochloride accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of Terbinafine Hydrochloride after 12 days was 73 μg/g and 7 days after cessation of treatment the concentration was still 5.8 μg/g. At the 150 mg once-a-week dose, the concentration of Terbinafine Hydrochloride in stratum corneum on day 7 was 23.4 μg/g and 7 days after the second dose was still 7.1 μg/g. Concentration of Terbinafine Hydrochloride in nails after 4 months of 150 mg once-a-week dosing was 4.05 μg/g in healthy and 1.8 μg/g in diseased nails; and, Terbinafine Hydrochloride was still measurable in nail samples 6 months after the end of therapy.

Biotransformation: Terbinafine Hydrochloride is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Terbinafine Hydrochloride is a selective inhibitor of the isozymes CYP2C9 and CYP3A4. Terbinafine Hydrochloride is also an inhibitor of the isozyme CYP2C19.

Excretion: Plasma elimination half-life for Terbinafine Hydrochloride is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. Terbinafine Hydrochloride clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites. The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.

Pharmacokinetics in renal impairment: In patients with severe renal insufficiency, (GFR< 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Terbinafine Hydrochloride is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of Terbinafine Hydrochloride is eliminated from blood.

Pharmacokinetics in children: Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study. After administration of 2-8 mg/kg Terbinafine Hydrochloride to children between the ages of 9 months to 15 years, an AUC of about 38 µg•h/ml was found per 1 mg/kg dose units.. The average Terbinafine Hydrochloride plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher Terbinafine Hydrochloride plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the Terbinafine Hydrochloride plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg. Experience with Terbinafine Hydrochloride in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of Terbinafine Hydrochloride were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-

1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040- 1680) on day 13.

Pharmacokinetics in elderly: A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of Terbinafine Hydrochloride. Ten of these patients were concomitantly receiving diuretics. The Cmax was 1.54 µg/ml and occurred at 1.3 hours postdose. The mean AUC was 76.4 ± 20.3 µg•h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Co administation of diuretics did not significantly alter AUC or Cmax. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the Terbinafine Hydrochloride renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of Terbinafine Hydrochloride disposition in the elderly appears to be related to reduced renal function characteristics of this group.

4.3 Preclinical safety Data: Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

Carcinogenesis: Terbinafine Hydrochloride showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 27 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Reproductive toxicity: Terbinafine Hydrochloride did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg. There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification. The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a

few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of Terbinafine Hydrochloride. Such a hormone change has not been observed in women treated with Terbinafine Hydrochloride

5. Pharmaceutical Particulars:

5.1 List of excipients:

Cross carmelose
Sodium Lauryl
Sulphate Sodium
Lauryl Sulphate
Purified Water
Crosspovidone
Aeo
sil
Talc
um

5.2 Incompatibilities

Not known

5.3 Shelf life

36 Months

5.4 Special precautions for storage

Store below 30°C in dry place. Protect from light.

5.5 Nature and contents of container:

Alu-Alu blisters of 7 Tablets.

Such 2 blister is packed in a carton along with pack insert.

5.6 Special Precaution for Disposal and other handling:

None

6. Marketing Authorization Holder and Manufacturing Site Address:

Coral Laboratories Limited

#3B, Patanwala Compound, Opp. Shreyas Cinema,

L.B.S. Marg, Ghatkopar (West),

Mumbai – 400 086, INDIA

Manufacturing Site

(Company) Name: CORAL LABORATORIES LIMITED

Address : Plot No. 57/1 (16), Bhenslore,

Dunetha, Nani Daman – 396210 INDIA

Email : exports@corallab.com

Website : www.corallab.com

7. Marketing Authorization Numbers

CTD13444

8. Date of first Registration /renewal of the Registration

06/03/2026

9. Date of revision of the text

06/03/2026