

# New Zealand Datasheet

## 1 PRODUCT NAME

Terbinafine-DRLA tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Terbinafine hydrochloride 250 mg tablets

## 3 PHARMACEUTICAL FORM

Terbinafine-DRLA 250 mg tablets: White to off-white, round flat bevelled edge tablets, embossed with 'R250' on one side and a score line on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Onychomycosis (fungal infection of the nail) caused by dermatophyte fungi.
- Tinea capitis.
- Fungal infections of the skin for the treatment of 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.

Note: Oral terbinafine is not effective in Pityriasis versicolor.

### 4.2 Dose and method of administration

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

Do not divide the tablets into quarters. The product is not able to deliver all approved dose regimens

#### Children

No data are available in children under two years of age (usually < 12 kg)

Children weighing <20 kg: 62.5 mg once a day.

Children weighing 20 to 40 kg: 125 mg once a day.

Children weighing >40 kg: 250 mg once a day.

#### Adults

250 mg once a day.

#### Skin Infections

Recommended duration of treatment:

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

Tinea corporis, cruris: 2 to 4 weeks.

Cutaneous candidiasis: 2 to 4 weeks.

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

#### Hair and scalp infections

Recommended duration of treatment:

Tinea capitis: 4 weeks

Tinea capitis occurs primarily in children.

### **Onychomycosis**

For most patients the duration of successful treatment is 6-12 weeks.

### **Fingernail onychomycosis**

Six weeks of therapy is usually sufficient for fingernail infections in most cases.

### **Toenail onychomycosis**

Twelve weeks of therapy is sufficient for toenail infection in most cases. Some patients with poor nail outgrowth may require longer treatment. The optimal clinical effect is seen some months after mycological cure and cessation of treatment. This is related to the period required for the outgrowth of healthy nail.

### **Use of Terbinafine-DRLA tablets in the elderly.**

Elderly patients generally do not experience any different side effects than younger patients and there is no evidence to suggest that elderly patients require different dosages than younger patients. Pre existing impairment of liver or kidney function should be considered in treatment of patients in this age group.

### **Use of Terbinafine-DRLA tablets in children**

In children above 2 years of age, oral terbinafine has been found to be well tolerated.

## **4.3 Contraindications**

Known hypersensitivity to terbinafine or to any of the excipients.

## **4.4 Special warnings and precautions for use**

### **Impaired hepatic function**

Terbinafine-DRLA tablets are not recommended for patients with chronic or active liver disease. Before prescribing Terbinafine-DRLA tablets, patients should be assessed for pre-existing liver disease. Hepatotoxicity may occur in patients with or without pre-existing liver disease. Rare cases of liver failure, some leading to death or liver transplant, have occurred with the use of Terbinafine-DRLA tablets for the treatment of onychomycosis in individuals with or without pre-existing liver disease. (see Adverse Effects). Patients prescribed Terbinafine-DRLA tablets should be warned to report immediately any symptoms of persistent nausea, anorexia, fatigue, vomiting, right upper abdominal pain or jaundice, dark urine or pale stools. Patients with these symptoms should discontinue taking oral terbinafine and the patient's liver function should be immediately evaluated.

### **Patients with impaired renal function**

Patients with impaired renal function (creatinine clearance less than 50 ml/min or serum creatinine of more than 300 micromol/l) should receive half of the normal dose (see Adverse Effects). There is no experience on the use of Terbinafine-DRLA tablets in patients with creatinine clearance values less than 20 ml/min.

### **Effects on blood**

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

terbinafine tablets. Patients taking terbinafine tablets should be advised to report any symptoms of infections.

#### **Effects on lymphocyte counts (ALC)**

Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. In placebo-controlled trials, 8/465 terbinafine-treated patients (1.7%) and 3/137 placebo treated patients (2.2%) had decreases in ALC to below 1000/mm<sup>3</sup> on two or more occasions. The clinical significance of this observation is unknown. However, in patients with known or suspected immunodeficiency, physician should consider monitoring complete blood counts in individuals using Terbinafine-DRLA tablets for greater than six weeks.

#### **Effect on vision**

During high-dose studies in monkeys, refractile irregularities were observed in the retina at doses that were 30 to 60 times the human dose (non-toxic effect level 50 mg/kg). The clinical relevance of this observation is unknown. However, the ocular effects in monkeys were not confirmed in humans in the placebo-controlled trials, where the incidence of ophthalmic abnormalities was lower in the terbinafine-treated patients (1.1 %) compared with those who received placebo (1.5 %).

#### **Dermatological effects**

Serious skin reactions (e.g., Stevens - Johnson syndrome and toxic epidermal necrosis) have been very rarely reported in patients taking terbinafine tablets. If progressive skin rash occurs, treatment with Terbinafine-DRLA tablets should be discontinued.

#### **Effects on lipids**

In chronic toxicity studies in rats, oral terbinafine, at dose of 309 mg/kg per day, increased serum cholesterol levels. This effect was more marked in female, than in male, rats. Effects on triglyceride levels were not consistent among the various studies. In monkeys a daily dose of 300 mg/kg increased triglyceride levels and chylomicron concentrations. In a small clinical study a daily dose of 250 mg for 8 weeks did not result in detectable changes in the plasma lipid profile. In other clinical trials there was no evidence of a significant change in plasma lipid profile of patients.

#### **Inhibition of CYP2D6 metabolism**

In vitro and in vivo studies have shown that terbinafine inhibits CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolised by this enzyme, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics class 1C and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed up if the co-administered drug has a narrow therapeutic window (see interactions) .

Terbinafine-DRLA tablets should be kept out of reach of children.

### **4.5 Interaction with other medicines 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 Terbinafine-DRLA 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***

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 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.

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 Terbinafine-DRLA tablets 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 compounds predominantly metabolised by this enzyme, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs),  $\beta$ -blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics class 1C and monoamine oxidase inhibitors (MAO-Is) Type B, and if they also have a narrow therapeutic window (see Warnings and Precautions).

Terbinafine decreased the clearance of desipramine by 82%.

In studies in healthy subjects characterized as extensive metabolisers 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 metabolisers to poor metaboliser status.

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

Terbinafine increased the clearance of cyclosporin by 15%.

## 4.6 Fertility, pregnancy and lactation

Pregnancy Category: B1

Though foetal toxicity and fertility studies have shown no adverse effects in animals, there is very limited information with Terbinafine-DRLA tablets in pregnant women; therefore, unless the potential benefits outweigh any potential risks, Terbinafine-DRLA tablets should not be used during pregnancy.

Terbinafine is excreted in breast milk; therefore mothers receiving Terbinafine-DRLA tablets should not breastfeed.

## 4.7 Effects on ability to drive and use machines

There is no data on whether Terbinafine-DRLA tablets affects the ability to drive or operate machinery.

## 4.8 Undesirable effects

Frequency estimate: very common  $\geq 10\%$ , common  $\geq 1\%$  to  $<10\%$ , uncommon  $\geq 0.1\%$  to  $<1\%$ , rare  $\geq 0.01\%$  to  $<0.1\%$ , very rare  $<0.01\%$ .

In general, terbinafine is well tolerated. Side effects are mild to moderate in severity, and transient. The following adverse reactions have been observed in the clinical trials or during post marketing experience.

### *Blood and lymphatic system disorders*

Very rare: Haematological disorders such as neutropenia, agranulocytosis, thrombocytopenia, pancytopenia and allergic reactions (including anaphylaxis).

### *Immune system disorders*

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

### *Nervous system disorders*

Common: Headache.

Uncommon: Taste disturbances, including taste loss, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged taste disturbances have been reported. A decrease of food intake leading to significant weight loss was observed in very few severe cases.

Very rare: Dizziness, paraesthesia and hypoaesthesia.

### *Gastrointestinal disorders*

Very common: Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).

### *Hepatobiliary disorders*

Rare: Hepatobiliary dysfunction (primarily cholestatic in nature), including very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant).

### *Skin and subcutaneous tissue disorders*

Very common: Non-serious forms of skin reactions (rash, urticaria).

Very rare: Psoriasiform eruptions or exacerbation of psoriasis. Hair loss, although a causal relationship has not been established. Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalized exanthematous pustulosis, anaphylactoid reactions including

angioedema). In the event of an allergic or severe skin reaction, terbinafine treatment should be discontinued.

*Musculoskeletal and connective tissue disorders*

Very common: Musculoskeletal reactions (arthralgia, myalgia).

*General disorders*

Very rare: Fatigue.

**Other adverse drug reactions from post-marketing spontaneous reports**

The following adverse drug reactions have been identified based on post-marketing spontaneous reports and are organized by system organ classes. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

*Blood and lymphatic system disorders:* anaemia.

*Immune system disorders:* anaphylactic reaction, serum sickness-like reaction.

*Vascular disorders:* vasculitis.

*Nervous system disorders:* anosmia including permanent anosmia, hyposmia.

*Skin and subcutaneous tissue disorders:* photosensitivity reactions (e.g. photodermatitis, photosensitivity allergic reaction and polymorphic light eruption)

*Ear and labyrinth disorders:* hypoacusis, impaired hearing, tinnitus

*Gastrointestinal disorders:* pancreatitis

*Musculoskeletal and connective tissue disorders:* rhabdomyolysis.

*General disorders and administration site conditions:* influenza-like illness, pyrexia.

*Investigations:* blood creatine phosphokinase increased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## 4.9 Overdose

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.

In case of overdose, immediately contact the Poisons Information Centre for advice, in New Zealand, call 0800 764 766.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungals for systemic use, ATC-code: D01BA02

Terbinafine is an allylamine with a broad spectrum of antifungal activity. At low concentrations, Terbinafine is fungicidal against dermatophytes such as *Trichophyton* (eg. *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*, moulds and certain dimorphic fungi. The activity against yeasts is fungicidal or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not a cytochrome P450 enzyme. Its inhibition leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. When given orally, the drug concentrates rapidly in skin, hair and nails at levels associated with fungicidal activity.

Metabolism of hormones and other drugs is not affected by treatment with Terbinafine-DRLA tablets.

### 5.2 Pharmacokinetic properties

Following oral administration, terbinafine is well absorbed (>70 %) and the absolute bioavailability of terbinafine from tablets as a result of first-pass metabolism is approximately 50 %. 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, 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. From the increase in plasma AUC an effective half-life of ~30 hours can be calculated. The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20 %), but not sufficiently to require dose adjustments.

Terbinafine binds strongly to plasma proteins (99 %). It rapidly diffuses through the dermis and concentrates 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.

Terbinafine is metabolised 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, which are excreted predominantly in the urine. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been observed.

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 %.

### 5.2 Pharmacokinetic properties

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 tumours 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, refractile 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. They were not associated with histological changes.

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 PARTICULARS**

### **6.1 List of excipients**

Magnesium stearate, silica colloidal anhydrous, hypromellose, croscarmellose sodium, microcrystalline cellulose.

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

36 months.

### **6.4 Special precautions for storage**

Store below 25°C.

### **6.5 Nature and contents of container**

Terbinafine-DRLA 250 mg tablets: PVC/PVDC blister packs containing 14, 28 or 42 tablets.

### **6.6 Special precautions for disposal**

No special requirements

## **7 MEDICINE SCHEDULE**

Prescription Medicine

## **8 SPONSOR**

Dr Reddy's New Zealand Ltd  
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**9 DATE OF FIRST APPROVAL**

9 October 2008

**10 DATE OF REVISION OF THE TEXT**

2 June 2017

**SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>