

New Zealand Datasheet

Name of Medicine

Terbinafine tablets

Terbinafine hydrochloride 250 mg tablets

Presentation

Terbinafine 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.

Uses

Actions

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 tablets.

Pharmacokinetics

A mean peak plasma concentration of 1.3mcg/ml is achieved with a single - oral dose of 250 mg within two hours after Terbinafine tablet administration. Gastrointestinal tract absorbs 70% of the dose. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours. The peak plasma concentration and bioavailability (AUC) roughly double when steady state is reached at 10-14 days. The bioavailability of Terbinafine tablets is moderately increased (20%) by food, but not sufficiently to require dosing adjustments.

Terbinafine is lipophilic and binds strongly to plasma proteins (99%). Terbinafine is widely distributed in the body including adipose tissue. It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentration in hair follicles, hair and sebum-reach skin. There is evidence that Terbinafine is distributed into the nail plate within the first few weeks of commencing therapy.

Terbinafine is excreted mainly in urine (80%) and in faeces (20%). The liver metabolizes absorbed terbinafine rapidly and extensively. At least seven cytochrome P450 isoenzymes (CYP 2C9, CYP 1A2, CYP 3A4, CYP 2C8, and CYP 2C19) are involved in its metabolism. Terbinafine inhibits, but is not metabolized by CYP 2D6. As a result of terbinafine biotransformation at least 15 identified metabolites are formed. These metabolites lack antifungal activity and they are excreted in the urine.

The plasma elimination half-life is 17 hours and the terminal half-life in stratum corneum, nail, hair, dermis and epidermis ranges from 22 to 28 days. There is no evidence of accumulation. Higher plasma concentrations were noted in older adults and in hypertensives and lower concentrations were noted in smokers. Age was not observed as a factor for changes in plasma concentrations of terbinafine, but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in higher blood levels of terbinafine.

In pharmacokinetic 250 mg single dose studies in patients with pre-existing liver disease it was shown that the clearance of terbinafine may be reduced by about 40%.

In pharmacokinetic 250 mg single dose studies on renally impaired patients (median creatinine clearance of 17.6 ml/sec), terbinafine clearance was halved resulting in a doubling or more of peak plasma concentrations or AUC. There was no direct correlation between creatinine clearance and terbinafine clearance in renally impaired patients, the metabolism of the drug having been impaired in these patients due to competition between metabolite and parent drug.

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.

Dosage and 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 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 tablets in children

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

Contraindications

Known hypersensitivity to terbinafine or to any of the excipients.

Warnings and Precautions

Impaired hepatic function

Terbinafine tablets are not recommended for patients with chronic or active liver disease. Before prescribing terbinafine 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 tablets for the treatment of onychomycosis in individuals with or without pre-existing liver disease. (see Adverse Effects). Patients prescribed terbinafine 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 tablets in patients with creatinine clearance values less than 20 ml/min.

Effects on blood

Patients taking terbinafine tablets are at risk of developing agranulocytosis, neutropenia and pancytopenia which are associated rarely with terbinafine. The problem usually resolves within a few days to a week of withdrawal of terbinafine. Patients taking terbinafine tablets should be advised to report any symptoms of

infections. Prescribers should examine the patient to determine the correct aetiology of any blood dyscrasias that occur in patients treated with terbinafine tablets.

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/mm³ 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 tablets for greater than six weeks.

Effect on vision

Changes in the ocular lens and retina have been reported following the use of terbinafine tablets in controlled trials. The clinical significance of these changes is unknown.

Dermatological effects

There have been isolated reports of serious skin reactions (e.g., Stevens - Johnson syndrome and toxic epidermal necrosis). If progressive skin rash occurs, treatment with terbinafine 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 tablets should be kept out of reach of children.

Use in 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 tablets in pregnant women; therefore, unless the potential benefits outweigh any potential risks, Terbinafine tablets should not be used during pregnancy.

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

Effects on Ability to Drive and Use Machines

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

Adverse 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 most common are gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea), non-serious forms of skin reactions (rash, urticaria), musculoskeletal reactions (arthralgia, myalgia).

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.

Rare: Hepatobiliary dysfunction (primarily cholestatic in nature) has been reported in association with terbinafine treatment, including very rare cases of serious liver failure, some with a fatal outcome, or requiring liver transplant (see Warnings and Precautions).

Very rare: Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), acute generalised exanthematous pustulosis, and anaphylactoid reactions (including angioedema) have been reported. In the event of an allergic or severe skin reaction, terbinafine treatment should be discontinued. Psoriasiform eruptions or exacerbation of psoriasis has been reported.

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

Very rare: headache and dizziness have been observed, for which the causal relationship has not been established.

Very rare: hair loss has been reported, although a causal relationship has not been established.

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.

Gastrointestinal disorders: pancreatitis

Musculoskeletal and connective tissue disorders: rhabdomyolysis.

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

Investigations: blood creatine phosphokinase increased.

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 Terbinafine 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%.

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.

Some cases of menstrual irregularities have been reported in patients taking Terbinafine 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), β -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 Special warnings and special precautions for use).

Terbinafine decreased the clearance of desipramine by 82%.

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

Terbinafine increased the clearance of cyclosporin by 15%.

Overdosage

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.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Prescription Medicine

Package Quantities

Terbinafine 250 mg tablets: packs containing 14 or 28 tablets.

Further Information.

List of excipients

Magnesium stearate, Silica colloidal anhydrous, Hypromellose, Croscarmellose sodium, Microcrystalline cellulose.

Incompatibilities

None known.

Preclinical safety data

In long-term studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver 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.

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