

DATA SHEET

Terbinafine-DP

Terbinafine 250 mg, as Terbinafine hydrochloride

Presentation

White, round, flat tablets embossed 'T250' on one side and a score on the other side.

Uses

Actions

Pharmacodynamic properties

Pharmacotherapeutic group: Oral antifungal agent (ATC code D01B A02).

Terbinafine is an allylamine which has a broad spectrum of activity against fungal pathogens of the skin, hair and nails including dermatophytes such as *Trichophyton* (e.g. *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*. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. Its activity against yeasts is fungicidal or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system. Terbinafine does not influence the metabolism of hormones or other drugs.

When given orally, the drug concentrates in skin, hair and nails at levels associated with fungicidal activity.

Pharmacokinetics

A single oral dose of 250 mg terbinafine results in peak plasma concentrations of 0.97 microgram/mL within 2 hours of administration. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours. The bioavailability of terbinafine is moderately affected by food, 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, and CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. The terminal elimination half-life is 17 hours. There is no evidence of accumulation. No age-dependent changes in steady-state plasma concentrations of terbinafine have been observed, but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in higher blood levels of terbinafine.

Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of Terbinafine-DP may be reduced by about 50%.

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: In contrast to topical Terbinafine, oral Terbinafine-DP is not effective in pityriasis versicolor.

Dosage and Administration

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

Children

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

Children weighing < 20 kg 62.5 mg

Children weighing 20 to 40 kg 125 mg

Children weighing > 40 kg 250 mg

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 sufficient for fingernail infections in most cases.

Toenail onychomycosis

Twelve weeks of therapy is sufficient for toenail infections 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 outgrowth of healthy nail.

Use of Terbinafine 250 in the elderly

There is no evidence to suggest that elderly patients require different dosages or experience different side effects than younger patients. When prescribing tablets for patients in this age group, the possibility of pre-existing impairment of liver or kidney function should be considered (see Warnings and Precautions).

Use of Terbinafine 250 in children

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

Contraindications

Hypersensitivity to terbinafine hydrochloride and any of the excipients.

Warnings and Precautions

Impaired hepatic function

Terbinafine-DP tablets are not recommended for patients with chronic or active liver disease. Before prescribing Terbinafine-DP tablets, pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and 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-DP 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 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.

Effect 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.

Effect 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, physicians 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 necrolysis). If progressive skin rash occurs, treatment with terbinafine tablets should be discontinued.

Effect on lipids

In chronic toxicity studies in rats, oral terbinafine, at a 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 the 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, such as 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).

Use during pregnancy and lactation

Foetal toxicity and fertility studies in animals suggest no adverse effects. Since clinical experience in pregnant women is very limited, Terbinafine-DP should not be used during pregnancy unless the potential benefits outweigh any potential risks.

Terbinafine is excreted in breast milk; mothers receiving oral treatment with Terbinafine-DP should therefore not breast-feed.

Effects on ability to drive and use machines

There are no data on whether Terbinafine-DP affects the ability to drive and use machines.

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-DP tablets are well tolerated. Side effects are usually mild to moderate 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-DP 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-DP treatment should be discontinued. Psoriasisiform 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

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. cyclosporin, terfenadine, triazolam, tolbutamide or oral contraceptives).

In vitro studies have shown however, that terbinafine inhibits the CYP2D6-mediated metabolism. This *in vitro* finding may be of clinical relevance for compounds predominantly metabolised by this enzyme, such as tricyclic antidepressants (TCAs), β -blockers, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAO-Is) Type B, and if they also have a narrow therapeutic window (see Warnings and Precautions).

Some cases of menstrual irregularities have been reported in patients taking Terbinafine-DP concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone. On the other hand, the plasma clearance of terbinafine may be accelerated by drugs, which induce metabolism (such as rifampicin) and may be inhibited by drugs, which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such agents is necessary, the dosage of Terbinafine-DP may need to be adjusted accordingly.

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 in eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy, if needed.

Pharmaceutical Precautions

Keep out of reach of children.

Shelf life of 36 months when stored below 25°C. Protect from light and moisture.

Medicine Classification

Prescription Medicine

Package Quantities

Packs of 14, 28, 42, 100, 150, 200, 250, 300, 350, 400, 450 and 500 are available in blisters and bottle packs.

Further Information

Terbinafine hydrochloride has a molecular mass of 327.90 and molecular formula of $C_{21}H_{26}ClN$. The other ingredients found in Terbinafine-DP tablets are microcrystalline cellulose, croscarmellose sodium, hypromellose, colloidal silicon dioxide and magnesium stearate.

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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