

Terbinafine - oral

Core Safety Profile

4. CLINICAL PARTICULARS

4.2 Posology and method of administration

Additional information on special population

Liver impairment

Terbinafine tablets are not recommended for patients with chronic or active hepatic disease (see section 4.4 Special warnings and precautions for use).

Renal impairment

Use of terbinafine tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Elderly

There is no evidence to suggest that elderly patients require different dosages or experience different side effects than younger patients. When prescribing terbinafine tablets for patients in this age group, the possibility of pre-existing impairment of hepatic or kidney function should be considered (see section 4.4. Special warnings and precautions for use).

Children

Only for products approved in the paediatric population:

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

4.3 Contraindications

Known hypersensitivity to terbinafine or to any of the excipients of terbinafine tablets.

4.4 Special warnings and precautions for use

Liver function

Terbinafine tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing terbinafine tablets, liver function test should be performed. Hepatotoxicity may occur in patients with and without pre-existing hepatic disease therefore periodic monitoring (after 4-6 weeks of treatment) of liver function test is recommended. Terbinafine should be immediately discontinued in case of elevation of liver function test. Very rare cases of serious hepatic failure (some with a fatal outcome, or requiring hepatic transplant) have been reported in patients treated with terbinafine tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine tablets was uncertain. (see section 4.8 Undesirable effects).

Patients prescribed terbinafine tablets should be warned to report immediately any signs and symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine or pale faeces. Patients with these symptoms should discontinue taking oral terbinafine and the patient's hepatic function should be immediately evaluated.

Dermatological effects

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

Haematological effects

Very rare cases of blood disorders (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with terbinafine tablets. Aetiology of any blood disorders 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.

Renal function

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micro mol/L) the use of terbinafine tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties).

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as very rare cases of lupus erythematosus have been reported.

Other

Terbinafine 125 mg tablets contain lactose (21 mg/tablet). Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take terbinafine 125 mg tablets.

4.5 Interaction with other medicinal products 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 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.

Some cases of irregular menstruation 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 CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, especially if they also have a narrow therapeutic window (see 4.4. Special warnings and 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 ciclosporin by 15%.

4.6 Fertility, pregnancy and lactation

Pregnancy

Foetal toxicity and fertility studies in animals suggest no adverse effects. Since clinical experience in pregnant women is very limited, terbinafine tablets should not be used during pregnancy unless clinical condition of the woman requires treatment with oral terbinafine and the potential benefits for the mother outweigh any potential risks for the foetus.

Lactation

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

Fertility

Foetal toxicity and fertility studies in animals suggest no adverse effects.

4.7 Effects on ability to drive and use machines

No studies on the effects of terbinafine tablets treatment on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects

The following adverse reactions have been observed in the clinical trials or during post marketing experience.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data)

Table 1

Blood and lymphatic system disorders	
<i>Very rare:</i>	Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia
<i>Not known:</i>	Anaemia.
Immune system disorders	
<i>Very rare:</i>	Anaphylactoid reaction, angioedema, cutaneous and systemic lupus erythematosus
<i>Not known:</i>	Anaphylactic reactions, serum sickness-like reaction
Metabolism and nutrition disorders	
<i>Very common:</i>	Decreased appetite
Psychiatric disorders	
<i>Not known:</i>	Anxiety, depression*
Nervous system disorders	
<i>Common:</i>	Headache
<i>Uncommon:</i>	Hypogeusia**, ageusia**
<i>Very rare:</i>	Dizziness, paraesthesia and hypoaesthesia
<i>Not known:</i>	Anosmia
Ear and labyrinth disorders	
<i>Not known:</i>	Hypoacusis, hearing impaired, tinnitus
Vascular disorders	
<i>Not known:</i>	Vasculitis
Gastrointestinal disorders	
<i>Very common:</i>	Abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea.
<i>Not known:</i>	Pancreatitis
Hepatobiliary disorders	
<i>Rare:</i>	Hepatic failure, hepatic enzymes increased
<i>Not known:</i>	hepatitis, jaundice, cholestasis
Skin and subcutaneous tissue disorders	
<i>Very common:</i>	Rash, urticaria
<i>Very rare:</i>	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP)). Psoriasiform eruptions or exacerbation of psoriasis. Alopecia,...

<i>Not known:</i>	Photosensitivity reaction, photodermatitis, photosensitivity allergic reaction and polymorphic light eruption
Musculoskeletal and connective tissue disorders	
<i>Very common:</i>	Arthralgia, myalgia
<i>Not known</i>	Rhabdomyolysis
General disorders and administration site conditions	
<i>Very rare:</i>	Fatigue
<i>Not known:</i>	Influenza like illness, pyrexia
Investigations	
<i>Not known:</i>	Blood creatinine phosphokinase increased, weight decreased ***

* Anxiety and depressive symptoms secondary to dysgeusia.

** Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.

*** *Weight decreased secondary to hypogeusia.

4.9 Overdose

A few cases of overdose (up to 5 g) have been reported, giving rise to headache, nausea, upper abdominal pain and dizziness. The recommended treatment of overdose consists of eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy, if needed.