AUSTRALIAN PRODUCT INFORMATION - NOUMED TERBINAFINE (TERBINAFINE)

1. NAME OF THE MEDICINE

Terbinafine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains terbinafine hydrochloride equivalent to 250 mg of terbinafine.

For the full list of excipients, see ***Section 6.1 List of excipients***.

3. PHARMACEUTICAL FORM

NOUMED TERBINAFINE 250 mg uncoated tablets are available as white to off-white, capsule shaped, biconvex tablets debossed with 'T' and '250' on either side of the breakline on one side and a deep breakline on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NOUMED TERBINAFINE is indicated for:

- Treatment in adults of ringworm (*tinea corporis, tinea cruris* and *tinea pedis*) due to infection caused by dermatophytes such as Trichophyton (e.g. *T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*, where oral therapy is considered appropriate owing to the site, severity or extent of the infection, and the infection is not responsive to topical therapy.
- Onychomycosis in adults (fungal infection of the nail) caused by dermatophyte fungi.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Recommended dosages and intervals

Terbinafine 250 mg tablet once a day, taken orally.
The bioavailability of terbinafine is not affected by a light meal.
The duration of treatment varies according to the indication and the severity of the infection.

Duration of treatment

Skin Infections

Likely durations of treatment are as follows: –

- Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks
- Tinea corporis, cruris: 2 to 4 weeks

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

Onychomycosis

For most patients the duration for successful treatment is between six weeks and three months.

Infections of finger and toenails (other than big toe) usually respond to the shorter duration of treatment, particularly in patients of younger age with a normal rate of nail outgrowth. In patients with slow nail growth, treatment for up to three months is usually adequate. However, infections in the big toe, or if nail growth is very poor, treatment for up to 6 months may be necessary.

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 tissue.

4.3 CONTRAINDICATIONS

Hypersensitivity to terbinafine or to any of the excipients in the formulation.
Severe, chronic or active hepatic disease (see ***Section 4.4 Special Warnings and Precautions for Use***).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Risk-benefit should be considered when the following medical problems exist:

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%).

Transient decreases in absolute lymphocyte counts (ALC)

Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. In placebo-controlled trials, 8/465 terbinafine tablets-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 therapy for greater than six weeks.

Effect on blood

Patients taking terbinafine tablets are at risk of developing agranulocytosis, thrombocytopenia, pancytopenia and neutropenia, which are very rarely associated with terbinafine. The problem usually resolves within a few days to a week of withdrawal of terbinafine tablets. Patients taking terbinafine tablets should be advised to report 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, and consideration should be given to a possible change in medication regimen, including discontinuation of treatment with terbinafine tablets.

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 triglycerides 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.

Dermatological effects

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

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as precipitation and exacerbation of psoriasis and cutaneous and systemic lupus erythematosus have been reported in a postmarketing setting.

Use in hepatic impairment

Terbinafine tablets are contraindicated for patients with chronic or active liver disease. Before prescribing terbinafine tablets, liver function tests should be performed since hepatotoxicity may occur in patients with and

without pre-existing liver disease. Therefore periodic monitoring (after 4-6 weeks of treatment) of liver function tests is recommended. Terbinafine should be immediately discontinued in case of elevation of liver function tests. Very rare cases of liver failure (some leading to liver transplant or death) have been reported with the use of terbinafine tablets. In the majority of hepatic failure cases, the patients had underlying systemic conditions (see ***Section 4.8 Adverse Effects (Undesirable 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.

Use in renal impairment

The use of terbinafine tablets in patients with impaired renal function (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micromol/L) has not been adequately studied and therefore terbinafine is not recommended.

Use in the elderly

There is no evidence to suggest that elderly patients require different dosages or experience side effects different from those in younger patients. When using terbinafine tablets in this age group, the possibility of impairment of liver or kidney function should be considered (see ***Section 4.4 Special Warnings and Precautions for Use***).

Paediatric use

There is no experience with terbinafine in children and its use cannot be recommended. Terbinafine tablets should be kept out of reach of children.

Effects on laboratory tests

Transient increases in serum urea, serum creatinine and liver enzymes.
Transient decreases in haematocrit, haemoglobin and leucocytes.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

There have been spontaneous reports of increase or decrease in prothrombin time in patients taking oral terbinafine and warfarin concomitantly. However, a causal relationship between terbinafine tablets and these changes has not been established.

Cautious use of terbinafine tablets is advised in women taking oral contraceptives since a few cases of menstrual disorders have been reported in patients taking this drug combination, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

The following medicinal products may increase the effect or plasma concentration of terbinafine

Cimetidine decreased the clearance of terbinafine by 33 %.

Fluconazole significantly increased the C_{max} and AUC of terbinafine, 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

In vitro and *in vivo* studies showed negligible potential for interaction with the drugs that are metabolised via the CYP450 system except those with CYP2D6-mediated metabolism (see below).

Terbinafine does not interfere with the clearance of **antipyrine or digoxin**. Terbinafine clearance is unaffected by **ciclosporin**.

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.

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

Compounds predominantly metabolised by CYP2D6

Terbinafine inhibits the CYP2D6-mediated metabolism, therefore patients receiving concomitant treatment with drugs predominantly metabolised by this enzyme, such as **tricyclic antidepressants (TCAs; e.g. desipramine), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics Class 1A, 1B and 1C, and monoamine oxidase inhibitors (MAOIs) Type B**, should be followed, especially if the co-administered drug has a narrow therapeutic window.

In studies in healthy subjects characterized as extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine significantly increased the dextromethorphan/dextrorphan metabolic ratio in urine. Thus, terbinafine may convert extensive CYP2D6 metabolisers to poor metaboliser status.

Caffeine - Terbinafine decreased the clearance of **caffeine** administered intravenously by 19%.

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

Ciclosporin - Terbinafine increased the clearance of ciclosporin by 15 %.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy

Category B1:

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Since clinical experience in pregnant women is not available, terbinafine tablets should not be used during pregnancy unless the potential benefits outweigh any potential risks.

Use in lactation

Terbinafine is excreted in breast milk. The ratio of terbinafine in milk to plasma is 7:1. Therefore, mothers receiving oral treatment with terbinafine tablets should not breast-feed.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In general terbinafine tablets are well tolerated. In clinical trials, adverse events occurred in 10.4% of patients taking terbinafine tablets and 5.6% of patients taking placebo. Most adverse events were mild to moderate in severity and of a short duration.

The following adverse reactions have been observed during clinical trials:

Frequency estimate: very common ≥ 10%; common ≥ 1% to < 10%; uncommon ≥ 0.1% to < 1%; rare ≥ 0.01% to < 0.1%; very rare < 0.01%.

Gastrointestinal disorders:
Very common: nausea, vomiting, flatulence, mild abdominal discomfort, abdominal cramps, anorexia, diarrhoea, dyspepsia/gastritis, belching, abdominal distension, decreased appetite.

Immune system disorders:
Very rare: anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus

Psychiatric disorders:
Common: depression
Uncommon: anxiety

Skin and subcutaneous tissue disorders:
Very common: urticaria, rash
Common: pruritus, erythema,
Uncommon: photosensitivity reactions
Very rare: psoriaform eruptions or exacerbation of psoriasis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis, toxic skin eruption, dermatitis exfoliative, dermatitis bullous, alopecia. In the event of an allergic or severe skin reaction, terbinafine tablet treatment should be discontinued.

Musculoskeletal and connective tissue disorders:
Very common : muscoskeletal reactions (arthralgia, myalgia)

Hepatobiliary disorders:
Rare: transient increases in liver enzymes, hepatobiliary dysfunction, cholestatic jaundice, liver failure (some leading to liver transplant or death). In the majority of liver failure cases, the patients had underlying systemic conditions (see ***Section 4.3 Contraindications***).

Blood and lymphatic system disorders:
Uncommon: anemia
Very rare: haematological disorders such as neutropenia, agranulocytosis, pancytopenia and thrombocytopenia

Nervous system disorders:
Very common: headache
Common: dysgeusia*, including ageusia*, dizziness, tiredness/fatigue
Uncommon: paraesthesia and hypoaesthesia
Very rare: sedation, light-headedness, chest pain.

Eye disorders:
Common: visual impairment

Ear and labyrinth disorders:
Uncommon: tinnitus

General disorders:
Uncommon: pyrexia

Investigations:
Uncommon: weight decreased**

*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 dysgeusia.

Postmarketing Data

Other adverse drug reactions from post-marketing spontaneous reports
The following adverse drug reactions have been derived from post-marketing experience with terbinafine via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as unknown. Adverse drug reactions are listed according to system organ classes in MedDRA.

Immune system disorders: anaphylactic reaction, serum sickness-like reaction
Psychiatric disorders: anxiety and depressive symptoms secondary to taste disturbances
Ear and labyrinth disorders: hypoacusis, impaired hearing
Eye disorders: vision blurred, visual acuity reduced
Vascular disorders: vasculitis
Nervous system disorders: anosmia including permanent anosmia, hyposmia
Skin and subcutaneous tissue disorders: drug rash with eosinophilia and systemic symptoms
Gastrointestinal disorders: pancreatitis
Musculoskeletal and connective tissue disorders: rhabdomyolysis
General disorders and administration site conditions: influenza-like illness
Investigations: blood creatine phosphokinase increased.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

A few cases of overdosage (up to 5 g) have been reported.

Signs and Symptoms

Studies in animals suggest that in a high-dose situation, such as accidental overdose, central nervous symptoms (CNS) may appear. The relevance of those effects to man is unknown. However, these effects can be monitored.

Central Nervous System: headache and dizziness
Gastrointestinal system: nausea and epigastric pain

Treatment

Give symptomatic supportive therapy, if needed.

The recommended treatment of overdosage consists in eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy, if needed. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Terbinafine is an allylamine with antifungal activity mainly against dermatophytes (e.g. *T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis*, and *Epidermophyton floccosum.*)

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.

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration, terbinafine is well absorbed (>70%) and the bioavailability of terbinafine hydrochloride tablets as a result of first-pass metabolism is approximately 40%. A single oral dose of 250 mg terbinafine results in peak plasma concentrations of 0.83 microgram/mL within two hours of administration. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours.

An increase in the AUC of terbinafine of less than 20% is observed when terbinafine tablets are administered with food. At steady-state, in comparison to a single dose, peak concentration of terbinafine is 25% higher and plasma AUC increases by a factor of 2.5. The increase in plasma AUC is consistent with an effective half-life of ~36 hours.

Distribution

Terbinafine binds strongly to plasma proteins (99%). It concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skins. There is also evidence from animal studies that terbinafine is distributed into the nail plate in the first few weeks after commencing therapy. Animal studies also indicate that terbinafine accumulates in all lipophilic tissues, including the retinal and choroid tissues. In studies conducted so far, no ophthalmological abnormalities attributable to terbinafine tablets have been reported in humans.

Metabolism

Terbinafine is extensively metabolised in the body. Biotransformation results in metabolites with no antifungal activity.

Excretion

Terbinafine and its metabolites are excreted predominantly in the urine. No age-dependent changes in pharmacokinetics have been observed. In patients with renal impairment (creatinine clearance ≤50 mL/min) or with pre-existing liver disease, the clearance of terbinafine is decreased by approximately 50% compared to normal volunteers.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

In a 2 year rat carcinogenicity study, small but significant increases in hepatocellular carcinomas, adenomas and combined tumours were seen in males at a dietary dose of 69 mg/kg per day. No increase in hepatic tumours was seen in female rats at a dietary dose of 97 mg/kg per day.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, sodium starch glycollate type A, hypromellose, colloidal anhydrous silica, magnesium stearate and purified talc.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/Al blister pack containing 14*, 28* and 42 tablets.

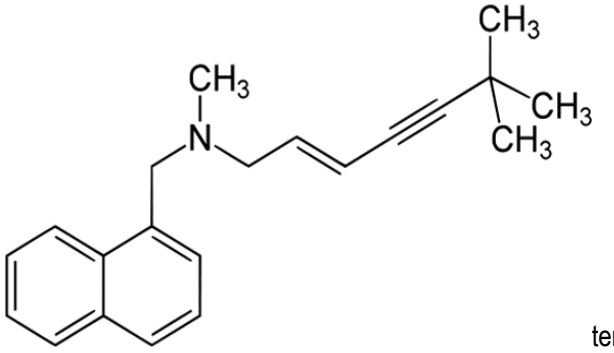
* Not currently distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

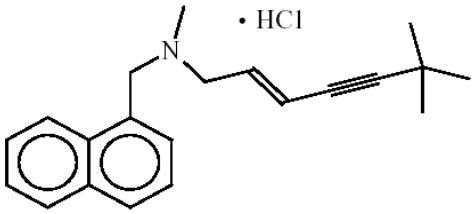
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



terbinafine base



terbinafine hydrochloride

Chemical name: terbinafine base: [(2E)-6,6-dimethylhept-2-en-4-yn-1-yl](methyl)(naphthalene-1-ylmethyl)amine; terbinafine hydrochloride: (E)-*N*-(6, 6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalenemethanamine

hydrochloride.

Molecular formula: terbinafine base: $C_{21}H_{25}N$; terbinafine hydrochloride: $C_{21}H_{26}ClN$

Molecular weight: terbinafine base: 291.40; terbinafine hydrochloride: 327.90

Terbinafine hydrochloride is a white or almost white powder. Very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone.

CAS number:

terbinafine base: 91161-71-6; terbinafine hydrochloride: 78628-80-5

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd.
Level 5, 7 Eden Park Drive
Macquarie Park NSW 2113

9. DATE OF FIRST APPROVAL

13 December 2019

10. DATE OF REVISION

24 March 2020

Summary table of changes

Section changed	Summary of new information
All	PI reformat
4.1, 4.4, 4.5, 4.7, 4.8, 5.1, 6.5	Minor editorial changes
4.4	Patient population reduced by contraindicating use in liver disease in line with 4.3
4.8	Frequency of anxiety, urticaria and rash increased
8	Update sponsor detail