

## **Arrow – Terbinafine**

Terbinafine hydrochloride 250 mg Tablets

---

### **Presentation**

---

Arrow - Terbinafine 250 mg Tablets are white to off-white, round uncoated tablet, scored on one side and marked "T" on the other side.

---

### **Clinical Particulars**

---

#### ***Actions***

Terbinafine is an allylamine with antifungal activity mainly against dermatophytes.

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 (CYP450) system. When given orally, the drug concentrates in skin and nails at levels associated with antifungal activity.

#### ***Pharmacokinetics***

Following oral administration, terbinafine is well absorbed (> 70%). A single oral dose of Arrow - Terbinafine 250 mg Tablet results in peak plasma concentrations of 1.1 µg/mL within two hours of administration. The area under the curve (AUC) is approximately 4.8 µg/mL.h. The absorption half-life of terbinafine 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 it is administered with food. At steady-state, in comparison to a single dose, the 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 approximately 36 hours.

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 have been reported in humans.

Terbinafine is extensively metabolised in the body. Biotransformation results in metabolites with no antifungal activity; in which are excreted predominantly in the urine. A plasma elimination half-life varying from 17 to 36 hours has been reported. No age dependent changes in pharmacokinetics have been observed. In patients with renal impairment (creatinine clearance ≤ 50 mL/min) or hepatic cirrhosis, the

clearance of terbinafine is decreased by approximately 50% compared to normal volunteers.

---

## **Indications**

---

Treatment 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 (fungal infection of the nail) caused by dermatophyte fungi.

---

## **Dosage and Administration**

---

### **Adults**

250 mg once a day, with or without food. The bioavailability of terbinafine is not affected by a light meal.

### **Children**

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

Children weighing < 20 kg      62.5 mg once daily

Children weighing 20 to 40 kg    125 mg once daily

Children weighing > 40 kg      250 mg once daily.

### **Renal impairment (see Warnings and Precautions)**

Half the normal dose (125 mg for adult) for creatinine clearance less than 50 mL/minute or serum creatinine more than 300 µmol/L.

### **Hepatic impairment (see Warnings and Precautions)**

Not recommended for patients with chronic or active liver disease.

This product is not able to deliver all approved dose regimens.

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

### **Skin infections**

Likely treatment durations are as follows:

Tinea pedis (interdigital, plantar or moccasin type): two to six weeks

Tinea corporis, cruris: two to four weeks

Tinea capitis (occurs primarily in children): four 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, for infections in the big toe, or if nail growth is very poor, treatment for up to six 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.

---

## **Contraindications**

---

Hypersensitivity to terbinafine or to any of the excipients in the formulation.

Severe hepatic disease (see **Warnings and Precautions**).

---

## **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 the normal dose (see **Adverse Effects**). There is no experience on the use of terbinafine tablets in patients with creatinine clearance value 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/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, 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.

### ***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 tablets in this age group, the possibility of impairment of liver and/or kidney function should be considered (see above).

### ***Carcinogenicity or mutagenicity***

In a two-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/day. No increase in hepatic tumours was seen in female rats at a dietary dose of 97 mg/kg/day.

### ***Use in pregnancy (Category B1)***

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

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because treatment of onychomycosis can be postponed until after pregnancy is completed, it is recommended that terbinafine not to be initiated during pregnancy.

### ***Use in lactation***

After oral administration, terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1. Treatment with terbinafine is not recommended in nursing mothers.

### ***Use in children***

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

### ***Effects on ability to drive and use machinery***

There is no data on whether Arrow – Terbinafine affects the ability to drive and/or use machinery.

### ***Pre-clinical 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.

---

## **Adverse Effects**

---

In general, terbinafine tablets are well tolerated. In clinical trials, adverse events occurred in 10.4% of patients taking terbinafine 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 and/or post-marketing surveillance. The frequency of adverse reactions is classified as very common: greater than or equal to 10%; common: greater than or equal to 1% to < 10%; uncommon: greater than or equal to 0.1% to < 1%; rare: greater than or equal to 0.01% to < 0.1%; and very rare < 0.01%.

### ***Gastrointestinal***

Very common: Nausea, vomiting, flatulence, abdominal discomfort, abdominal cramps, anorexia, diarrhoea, dyspepsia or gastritis, belching.

### ***Nervous system***

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.

### ***Musculoskeletal***

Very common: Arthralgia, myalgia.

### ***Dermatological***

Very Common: Urticaria, pruritus, erythema, rash.

Very rare: Psoriaform eruptions or exacerbation of psoriasis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, acute generalised exanthematous pustulosis. Hair loss, although a causal relationship has not been established.

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

### ***Immune system***

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

### ***Hepatic***

Rare: Transient increases in liver enzymes, hepatobiliary dysfunction, cholestatic jaundice.

Very rare: Liver failure, some leading to death or liver transplant (see **Warnings and Precautions**).

### ***Renal***

Rare: Transient rises in serum urea and/or serum creatinine.

### ***Haematological***

Transient decrease in haematocrit and/or haemoglobin; leucopenia.

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

### **Others**

Dizziness, tiredness or fatigue (very rare), sedation, light-headedness, chest pain.

### **Post-marketing experience**

The following events have been reported in association with terbinafine since market introduction:

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis

Investigations: Creatine phosphokinase (CPK) increase

Nervous System Disorders: Smell disorders including permanent anosmia

Immune System Disorders: Anaphylaxis, serum sickness-like reaction

Vascular Disorders: Vasculitis

General Disorders and Administration Site Conditions: Influenza-like illness, pyrexia

Gastrointestinal Disorders: Pancreatitis

Haematological Disorders: Anaemia

---

## **Interactions**

---

Terbinafine clearance is increased 100% by rifampicin, a CYP450 enzyme inducer, and decreased by 33% by cimetidine, a CYP450 enzyme inhibitor. Where co-administration of such agents is necessary, the dosage of terbinafine may need to be adjusted accordingly. Terbinafine clearance is unaffected by cyclosporin.

*In vitro* and *in vivo* studies have shown that terbinafine inhibits the CYP2D6 mediated metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolised by this enzyme, such as tricyclic antidepressants (e.g. desipramine), beta-blockers, selective serotonin reuptake inhibitors, anti-arrhythmics class 1C and monoamine oxidase inhibitors Type B, should be followed, if the co-administered drug has a narrow therapeutic window.

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

Terbinafine decreases the clearance of caffeine by 19% and increases the clearance of cyclosporin by 15%. Terbinafine does not interfere with the clearance of antipyrine or digoxin.

Cautious use of terbinafine is advised in women taking oral contraceptives since a few cases of menstrual disorders have been reported in patients taking this drug combination.

---

## **Overdosage**

---

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. 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.

---

## **Pharmaceutical Precautions**

---

### ***Storage***

Store below 25°C and protect from light

### ***Shelf life***

36 months

### ***Further information***

Keep out of reach of children

---

## **Medicine Classification**

---

Prescription-only medicine

---

## **Package Quantities**

---

Blister packs: 14's

Bottles: 100's

**Not all pack sizes or pack types may be marketed.**

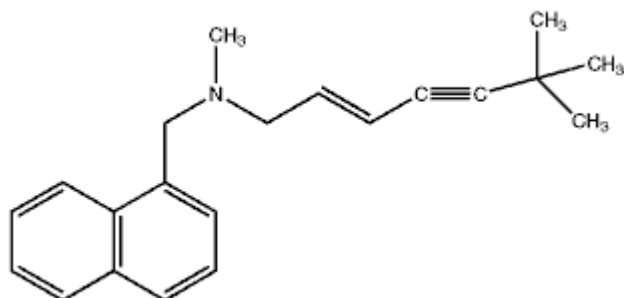
---

## **Further Information**

---

Arrow - Terbinafine is the hydrochloride salt of terbinafine.

The chemical name for terbinafine is (E)-N,6,6-trimethyl-N-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride. Its structural formula is:



• HCl

$C_{21}H_{25}N.HCl$       Molecular weight: 327.94      CAS No.: 78628-80-5

Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is soluble in isopropyl alcohol (> 70 mg/mL at 25<sup>0</sup>C) and ethanol (> 70 mg/mL at 25<sup>0</sup>C), and slightly soluble in water (6.3 mg/mL at 25<sup>0</sup>C).

ARROW - TERBINAFINE Tablets contain 250 mg of terbinafine (as hydrochloride). The tablets also contain microcrystalline cellulose, silicon dioxide, hypromellose, sodium starch glycollate and magnesium stearate. The tablets are gluten free.

---

## Name and Address

---

**Arrow Pharmaceuticals (NZ) Limited**  
Unit B8, Mt Eden Central Business Park  
31-49 Normanby Road, Mt Eden  
Auckland, New Zealand

---

## Date of Preparation

---

14March 2011