SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Terbinafine 250mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg terbinafine, as terbinafine hydrochloride
For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Round white to off-white flat bevelled edge tablet with a score line and R250 on reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of terbinafine sensitive fungal infections such as Tinea corporis, Tinea cruris and Tinea pedis caused by Dermatophytes is considered appropriate due to the site, severity or extent of the infection.

The treatment of onychomycosis (terbinafine-sensitive fungal infection of the nails) caused by dermatophytes.

Terbinafine Tablets are not effective against Pityriasis versicolor. The official local guidelines should be borne in mind, for example, national recommendations relating to the correct use and prescription of antimicrobial drugs.

4.2 Posology and method of administration

Route of administration: oral use

The tablets should not be divided and duration of treatment varies according to the indication and severity.

Adults: 250mg once daily

Patients with impaired renal function (creatinine clearance less than 50ml/minute or serum creatinine of more than 300micromol/l) should receive half the normal dose.

<u>Skin Infections</u>
Likely duration of treatment:

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

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

Onychomycosis
For most patients the duration of treatment is between 6 and 12 weeks. In most cases 6 weeks' treatment is sufficient in fingernail onychomycosis. Treatment periods of less than 12 weeks can be anticipated in younger patients or those with fingernail infections or toenail infections other than the big toe. 12 weeks is usually sufficient in the treatment of toenail infections although some patients may require 6 months treatment or longer.
Poor nail outgrowth during the first weeks of treatment may indicate those patients where longer therapy is required. The complete resolution of signs and symptoms of infection may not occur until several weeks after mycological cure.

Children and adolescents:	Not recommended due to lack of experience with oral terbinafine.
Use in the elderly:	There is no evidence to suggest that elderly patients require different dosages.

4.3 Contraindications

Known hypersensitivity to Terbinafine or any of the excipients.
Severe renal impairment.
Severe hepatic impairment.

4.4 Special warnings and precautions for use

Terbinafine tablets are not recommended for patients with chronic or active liver disease. Before prescribing Terbinafine tablets, any pre-existing liver disease should be assessed. Hepatotoxicity may occur in patients with and without pre-existing liver disease.

Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within 2 months of starting treatment. Patients prescribed terbinafine should be instructed to report immediately any signs or symptoms suggestive of liver dysfunction such as pruritis, persistent nausea, anorexia, tiredness, jaundice, vomiting, fatigue, abdominal pain, dark urine or pale stools (see Section 4.8). If a patient presents with such signs or symptoms liver function should be verified and treatment stopped. Single dose pharmacokinetic studies in patients with chronic or active liver disease indicate terbinafine clearance may be reduced by 50% (see section 5.2). The therapeutic use of Terbinafine in patients with chronic or active liver disease has not been studied in prospective clinical trials, and thus cannot be recommended.

Very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with terbinafine tablets. In the majority of reported liver failure cases, the patient had serious underlying systemic conditions and a causal association with the intake of terbinafine tablets was uncertain (see Section 4.8 Undesirable effects).

Terbinafine should be used with caution in patients with psoriasis, as very rarely cases of exacerbation have been reported.

Patients on terbinafine who develop a high fever or sore throat should be examined concerning possible haematological reactions.

Terbinafine is a potent inhibitor of the isoenzyme, CYP2D6, which should be considered if terbinafine is combined with medicinal products metabolised by this isoenzyme that are titrated individually (see section 4.5) and as such dose adjustments should be made as necessary.

4.5 Interaction with other medicinal products and other forms of interaction

The plasma clearance of terbinafine may be accelerated by medicinal products which induce metabolism (such as rifampicin) and may be inhibited by medicinal products which inhibit cytochrome P450 (such as cimetidine). Where the use of such medicinal products is necessary, the dosage may need to be adjusted accordingly.

Terbinafine inhibits the CYP2D6-mediated metabolism. This may be of relevance to patients receiving substances metabolised by this enzyme, such as tricyclic antidepressants, *B*-blockers, selective serotonin reuptake inhibitors, venlafaxine and monoamine oxidase inhibitors type B, whilst simultaneously taking terbinafine. These patients should be monitored. It should be noted that there may be a risk of clinically significant reactions for drugs metabolised by CYP2D6 for a few weeks after treatment with Terbinafine has been stopped.

Studies indicate terbinafine has negligible effect on the clearance of medicinal products that are metabolised via other cytochrome P450 enzymes (ciclosporin, tolbutamine, terfenadine, triazolam, oral contraceptives). However, some cases of menstrual disturbance (breakthrough bleeding and an irregular cycle) have been reported in patients taking terbinafine with oral contraceptives.
It should be noted that terbinafine causes a small but usually clinically unimportant reduction in ciclosporin serum levels. In general, the changes in the pharmacokinetics of ciclosporin appear to be clinically unimportant. However, patients whose ciclosporin levels are at the lower end of the therapeutic range should be closely monitored if they are given terbinafine.

Rare cases of changes in INR and/or prothrombin time have been reported in patients receiving terbinafine concomitantly with warfarin.

4.6 Pregnancy and lactation

Animal studies suggest that terbinafine has no undesirable effects.

Pregnancy:
There is no clinical experience of the use of terbinafine in pregnant women. Terbinafine should not be administered during pregnancy unless clearly necessary.

Lactation:
Terbinafine has been found to be excreted in breast milk and therefore nursing mothers should not receive terbinafine whilst breast feeding. Breast feeding should be discontinued before starting treatment with Terbinafine Tablets.

4.7 Effects on ability to drive and use machines

Terbinafine has no or negligible influence on the ability to drive or use machinery, however some of the undesirable effects which may be seen may impair the ability of the patient to react.

4.8 Undesirable effects

Adverse reactions are transient and generally mild to moderate in severity. The following adverse reactions have been observed and/or reported for terbinafine tablets.

Adverse reactions are ranked under headings of frequency using the following convention:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/ 10
Uncommon: ≥ 1/ 1,000 to < 1/ 100
Rare: ≥ 1/10,000 to < 1/ 1,000

Very rare: < 1/10,000
Not known: cannot be estimated from available data

Blood and lymphatic system disorders	
Very rare	Neutropenia, agranulocytosis, thrombocytopenia
Not known	Pancytopenia
Immune system disorders	
Very rare	Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus
Psychiatric disorders	
Very rare	Psychiatric disturbances (such as depression and anxiety)
Nervous system disorders	
Common	Headache
Uncommon	Taste disturbances, including taste loss, which usually recovers slowly after discontinuation of the drug. Very rare cases of prolonged taste disturbances have been reported (persisting up to 2 years after discontinuation of the drug), sometimes leading to a decrease of food intake and significant weight loss.
Rare	Paraesthesia, hypoaesthesia, dizziness
Ear and labyrinth disorders	
Very rare	Vertigo
Gastrointestinal disorders	
Very common	Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).
Hepatobiliary disorders	
Rare	Cases of serious hepatic dysfunction, including jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with terbinafine should be discontinued (see also Section 4.4 Special Warning and Precautions for Use).
Very rare	Very rare cases of serious liver failure have been reported (some with a fatal outcome or requiring liver transplant). In the majority of liver failure cases the patients had serious underlying systemic conditions.
Skin and subcutaneous tissue disorders	
Very common	Non-serious forms of skin reactions (rash, urticaria).
Very rare	Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity). If progressive skin rash occurs, terbinafine treatment should be discontinued.
Not Known	Psoriasiform eruptions or exacerbation of psoriasis. Serious skin reactions (e.g. acute generalized exanthematous pustulosis and Erythema Multiforme).
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal reactions (arthralgia, myalgia).
General disorders	

Rare	Malaise
Not known	Fatigue

4.9 Overdose

Reports of overdose are rare but a few cases have been reported where up to 5g has been taken giving rise to headache, nausea, epigastric pain and dizziness.

Treatment: Activated charcoal to adsorb and eliminate the terbinafine and symptomatic supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dermatologicals: antifungal for systemic use
ATC code: D01B A02

Terbinafine is a broad spectrum antifungal drug. At low concentrations terbinafine has fungicidal activity against dermatophytes, moulds and certain dimorphic fungi. Depending upon species, terbinafine demonstrates fungicidal or fungistatic activity against yeasts.

Terbinafine acts by interfering with fungal sterol biosynthesis at an early stage leading to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in cell death. Terbinafine also acts by inhibition of squalene epoxidase in the fungal cell membrane.

Terbinafine is used for the treatment of fungal infections of the skin and nails, which is caused by Trichophyton (e.g.T. rubrum, T.mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum.

5.2 Pharmacokinetic properties

A single oral dose of 250mg terbinafine results in mean peak plasma concentrations of 0.97mcg/ml within 2 hours after administration. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours. Terbinafine binds strongly to plasma proteins (99%).

Terbinafine rapidly diffuses through the skin and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and parts of the skin rich in sebaceous glands. There is also evidence that terbinafine is distributed into the nail plate within a few weeks after commencing therapy.

Terbinafine is rapidly metabolised by the CYP-isoenzymes, mainly by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. The elimination half-life is 17 hours. There is no evidence of accumulation in the plasma.

No age-dependent changes in pharmacokinetics have been observed but the elimination rate may be reduced in patients with renal or hepatic impairment, resulting in higher blood levels of terbinafine.

In patients with pre-existing mild to severe hepatic impairment, single dose pharmacokinetic studies have shown that the clearance of terbinafine can be reduced by 50%.

The bioavailability of terbinafine is only slightly affected by food, and therefore a dose adjustment is not necessary.

5.3 Preclinical safety data

The LD_{50} value of terbinafine is over 4 g/kg in both mice and rats.

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 100mg/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 dosage level of 69 mg/kg, at which systemic exposure was similar to clinical exposure. The mechanism of tumour development has not been established. The clinical relevance is unknown. The changes which may be associated with peroxisome proliferation have been shown to be species-specific since they were not seen in carcinogenicity study 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 50mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after discontinuation of the active substance. 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 undesirable effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Croscarmellose Sodium
Anhydrous Colloidal Silica
Hypromellose
Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

HDPE bottle: Do not store above 25°C. Store in the original package.
Blister pack: Do not store above 25°C. Keep blister in the outer carton.

6.5 Nature and contents of container

Aluminium foil/PVC/PVdC blisters in cartons of 14 or 28 tablets
White HDPE bottle with a polypropylene child resistant cap containing 60 or 500 tablets

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Dr. Reddy's Laboratories (UK) Ltd
6 Riverview Road
Beverley
HU17 0LD
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 08553/0186

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/01/2004

10. DATE OF REVISION OF THE TEXT

06/11/2011