TERBINAFINE 125MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0212

TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

UKPAR

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TERBINAFINE 125MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0212

TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

LAY SUMMARY

The MHRA granted Dr Reddy's Laboratories (UK) Limited Marketing Authorisations (licences) for the medicinal products Terbinafine 125mg Tablets (PL08553/0212) and Terbinafine 250mg Tablets (PL08553/0213) on 13th December 2005. These prescription only medicines (POM) are antifungals, used to treat a variety of fungal infections in the skin and nails in adults.

Terbinafine tablets contain the active ingredient terbinafine, as the hydrochloride salt, which is a broad-spectrum anti-fungal.

These applications are duplicates of previously granted applications for Terbinafine 125mg and 250mg Tablets (PL08553/0185-6) which had, in turn, demonstrated essential similarity or equivalence to the approved product, Lamisil 125mg and 250mg Tablets and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Terbinafine 125mg Tablets and Terbinafine 250mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

TERBINAFINE 125MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0212

TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Terbinafine 125mg Tablets (PL 08553/0212) and Terbinafine 250mg Tablets (PL08553/0213) to Dr Reddys Laboratories (UK) Ltd on 13 December 2005. The products are prescription only medicines.

The applications were submitted as informed consent abridged applications according to article 10.1(a)(i) of Directive 2001/83/EC, cross-referring to Terbinafine 125mg and 250mg Tablets (PL 08553/0185-6), approved on 8th January 2004. The referenced marketing authorisations were approved based on demonstration of essential similarity to Lamisil 125mg and 250mg Tablets, approved on 3rd October 1990.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference product. As the cross-reference products were granted prior to the introduction of current legislation, no PARs were generated for them.

The products contain the active ingredient terbinafine hydrochloride which is an antifungal agent indicated for the treatment of both nail and skin infections. Terbinafine tablets are indicated for dermatophyte infections of the nails, ringworm infections (including tinea pedis, cruris and corporis) when oral therapy is appropriate due to site, severity or extent.

These applications for Terbinafine 125mg Tablets and Terbinafine 250mg Tablets were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 08553/0212-213
PROPRIETARY NAME: Terbinafine 125mg and 250mg Tablets
ACTIVE(S): Terbinafine Hydrochloride
COMPANY NAME: Dr. Reddys
E.C. ARTICLE: Article 10.1(a)(i) of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION

These are 'piggy back' applications for Terbinafine 125mg and 250mg Tablets submitted under Article 10.1(a)(i) of Directive 2001/83/EC. The proposed MA holder is "Dr. Reddy's Laboratories (UK) Ltd, 6, Riverview Road, Beverley, East Yorks, HU17 0LD."

These applications cross refer to marketing authorisations for Terbinafine 125mg and 250mg tablets (PL 08553/0185-186) which are currently approved in the UK. These applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Terbinafine 125mg and 250mg Tablet. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain terbinafine hydrochloride equivalent to 125mg and 250mg of terbinafine respectively. They are to be stored in polyethylene containers of 60, 100 (125mg strength only) and 500 tablets or blister packs of 14 and 28 tablets. The proposed shelf-life (3 years) and storage conditions (Do not store above 25^{o}C; Keep in the original container; Keep blister in outer carton) are consistent with the details registered cross-reference products.

2.3 Legal status

On approval, the products will be subject to a medical prescription.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Dr. Reddy's Laboratories (UK) Ltd, 6, Riverview Road, Beverley, East Yorks, HU17 0LD

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference products.

2.9 Drug substance specification

The proposed drug substance specification for each product is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance

No materials of animal or human origin are included in the product. This is consistent with the cross reference products for which magnesium stearate was confirmed as being of vegetable origin.

3. EXPERT REPORTS

The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts' CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/CARTON

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

Carton and blister

The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The data submitted with the applications are acceptable. Marketing Authorisations should be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

As these are duplicate applications for PL 08553/0185-6, no new clinical data have been supplied and none are required.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications is consistent with that previously assessed for the cross-reference product and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Terbinafine is a well known drug and has been used as an anti-fungal agent for many years. These applications are identical to approved marketing authorisations for Terbinafine Tablets (PL08553/0185-6) in which the applicant demonstrated essential similarity to the innovator product, Lamisil 125mg and 250mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with terbinafine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

TERBINAFINE 125MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0212

TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 08/03/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 10/01/2005.
3	Following assessment of the application the MHRA requested further information on 08/02/2005, 28/06/2005, 02/08/2005 and 29/11/2005.
4	The applicant responded to the MHRA's requests, providing further information on 03/03/2005, 28/06/2005, 17/11/2005 and 09/12/2005
7	The application was determined on 13/12/2005

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TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

TERBINAFINE 125MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0212

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Terbinafine 125mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 125mg terbinafine, as terbinafine hydrochloride
For excipients see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Round white flat bevelled edge tablets with score line and R125 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.

Skin Infections
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

Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within 2 months of starting treatment. If a patient presents with signs or symptoms suggestive of liver dysfunction (pruritus, persistent nausea, anorexia, tiredness, or jaundice, vomiting, fatigue, abdominal pain or dark urine or pale stools, see section 4.8), 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.

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, and monoamine oxidase inhibitors type B, whilst simultaneously taking terbinafine. These patients should be monitored.

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.

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.

Common undesirable effects (>1/100, <1/10): dyspepsia, feeling full, loss of appetite, nausea, mild abdominal pain, diarrhoea, rash, urticaria, headache, malaise and fatigue. Musculo-skeletal disorders including arthralgia and myalgia have been reported. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

Uncommon undesirable effects (>1/1000, <1/100): ageusia and dysgeusia. Taste disturbances and loss have been reported in a small percentage of patients treated. However, this usually resolves slowly on discontinuation.

Rare undesirable effects (>1/10,000, <1/1,000): paraesthesia, hypoaesthesia, dizziness, anaphylactic reaction, serum sickness like reaction, angioneurotic oedema have been reported rarely. Rare cases of serious hepatic dysfunction, including jaundice, cholestasis, hepatitis and increased hepatic enzymes have been reported. If hepatic dysfunction develops, treatment should be discontinued.

Very rare undesirable effects (<1/10,000): vertigo, blood disorders such as neutropenia, thrombocytopenia and agranulocytosis, exacerbation of psoriasis and psychiatric disturbances such as depression and anxiety have been reported very rarely. In rare cases serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and hair loss) and appearance or aggravation of cutaneous or systemic lupus erythematosus have been reported. If a progressive skin rash occurs treatment should be discontinued. Menstrual disturbance (breakthrough bleeding and an irregular cycle) have also been reported in patients taking terbinafine concomitantly with oral contraceptives.

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 Pre-clinical 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, 100 or 500 tablets

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 08553/0212

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

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 flat bevelled edge tablets 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.

Skin Infections
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

Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within 2 months of starting treatment. If a patient presents with signs or symptoms suggestive of liver dysfunction (pruritus, persistent nausea, anorexia, tiredness, or jaundice, vomiting, fatigue, abdominal pain or dark urine or pale stools, see section 4.8), 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.

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.

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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.

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.

Common undesirable effects (>1/100, <1/10): dyspepsia, feeling full, loss of appetite, nausea, mild abdominal pain, diarrhoea, rash, urticaria, headache, malaise and fatigue. Musculo-skeletal disorders including arthralgia and myalgia have been reported. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

Uncommon undesirable effects (>1/1000, <1/100): ageusia and dysgeusia. Taste disturbances and loss have been reported in a small percentage of patients treated. However, this usually resolves slowly on discontinuation.

Rare undesirable effects (>1/10,000, <1/1,000): paraesthesia, hypoaesthesia, dizziness, anaphylactic reaction, serum sickness like reaction, angioneurotic oedema have been reported rarely. Rare cases of serious hepatic dysfunction, including jaundice, cholestasis, hepatitis and increased hepatic enzymes have been reported. If hepatic dysfunction develops, treatment should be discontinued.

Very rare undesirable effects (<1/10,000): vertigo, blood disorders such as neutropenia, thrombocytopenia and agranulocytosis, exacerbation of psoriasis and psychiatric disturbances such as depression and anxiety have been reported very rarely. In rare cases serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and hair loss) and appearance or aggravation of cutaneous or systemic lupus erythematosus have been reported. If a progressive skin rash occurs treatment should be discontinued. Menstrual disturbance (breakthrough bleeding and an irregular cycle) have also been reported in patients taking terbinafine concomitantly with oral contraceptives.

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 Pre-clinical 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 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 08553/0213

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

TERBINAFINE 125MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0212

TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

PRODUCT INFORMATION LEAFLET

Paper size: 270 x 90mm
Font: Frutegerlight 9

Component code

TERBINAFINE 125mg & 250mg TABLETS

PATIENT INFORMATION LEAFLET

Please read this leaflet carefully before you start taking this medicine. If you have any questions or are unsure about anything relating to your treatment, ask your doctor or pharmacist.

What you need to know about Terbinafine Tablets
The name of your medicine is Terbinafine Tablets. Terbinafine belongs to a family of medicines called antifungals. It is used in the treatment of a variety of fungal infections of the skin and nails in adults. The tablets contain terbinafine hydrochloride equivalent to 125mg or 250mg Terbinafine. The tablets also contain: magnesium stearate, colloidal anhydrous silica, hypromellose, microcrystalline cellulose and croscarmellose sodium. Both strengths are available in blister packs containing 14 or 28 tablets, and bottles containing 60 or 500 tablets. The 125mg is also available in bottles of 100 tablets.

Manufactured by the Authorisation Holder:

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

Before taking your medicine:
Tell your doctor before you start taking Terbinafine Tablets if any of the following apply to you:

- You suspect or know that you have had an allergic reaction to, any of the ingredients in Terbinafine
- You have any liver problems or have had any disease which may have affected your liver
- You have psoriasis
- You have any kidney problems
- Are you pregnant, or planning to become pregnant?
- You are breast-feeding

If you do become pregnant whilst taking terbinafine, tell your doctor.

If you are taking any other medicines (either bought or prescribed), you should be aware that some medicines can interfere with your treatment, so check with your doctor or pharmacist before taking any other medicines. In particular, tell your doctor if you are taking Rifampicin, Cimetidine, Oral contraceptives (as irregular periods and breakthrough bleeding may occur in some women), Antidepressants or any Beta-blocker drugs. If you suffer from a high fever or sore throat whilst taking Terbinafine Tablets consult your doctor.

Taking your medicine
Your doctor will decide the right dose for you and how long to take your tablets for. It is important that you complete the course of treatment, even if the infection heals.

Adults and the Elderly
The usual adult dose is 250mg a day but this may be reduced to 125mg a day. For skin infections take for between 2 to 6 weeks. For nail infections take for between 6 to 13 weeks, although some patients with toenail infections may need to take the tablets for 26 weeks or longer. Patients with kidney problems should be instructed to take half the usual adult dose.

Children and Adolescents
Not recommended.
Swallow your tablets whole with a glass of water. If you forget to take your tablet, take another as soon as you remember or wait until it is time to take your next dose. Then go on as before.

Overdose
If you accidentally take too much of your medicine, tell your doctor immediately, or go to your nearest casualty department, remember to take the tablets and packaging with you.

After taking your medicine
As with other medicines, Terbinafine Tablets may occasionally cause side effects in some patients. These are often mild to moderate and usually disappear after a while. The most common side effects include headache, loss of appetite, feeling sick, indigestion, diarrhoea, feeling full or mild abdominal pain, rash, itching, swelling, general feeling of being unwell or tiredness. Pains in the muscles and joints have been reported, usually with an allergic skin reaction such as swelling or rash.

A loss of taste and taste disturbances have been reported by a small number of patients. This usually only lasts whilst you are taking the tablets.

Rare side effects include feeling dizzy, diminished sense of touch, severe allergic reaction, unwell or tired and numbness or tingling. Rare side effects may include liver problems, including a yellowing of your skin, inflammation, increase liver enzymes or a severe skin rash (swelling, blistering or weals). If you notice any of these symptoms occurring stop taking your medication and tell your doctor immediately.

Very rarely people may experience a decrease in the number of some blood cells, depression and anxiety, vertigo or a worsening of psoriasis symptoms. Those taking oral

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Font: Frutegerlight 9

contraceptives should be aware that terbinafine may result in irregular bleeding. Serious skin reactions have been reported rarely including photosensitivity, hair loss, significant skin damage, Stevens-Johnson syndrome or the appearance or aggravation of areas of skin and tissue deformity. Treatment should be discontinued if a progressive skin rash arises.

The severity of some of these effects may affect your ability to drive or use machinery. You should tell your doctor or pharmacist about any other side effects not listed here.

Storing your medicine

Do not store above 25°C and store in the original packaging. In particular blisters should be kept in the outer carton. The packaging has a printed expiry date do not take these tablets if this date has passed. Keep your medicine in a safe place out of reach and sight of children. Any unused tablets should be returned to your pharmacist for safe disposal.

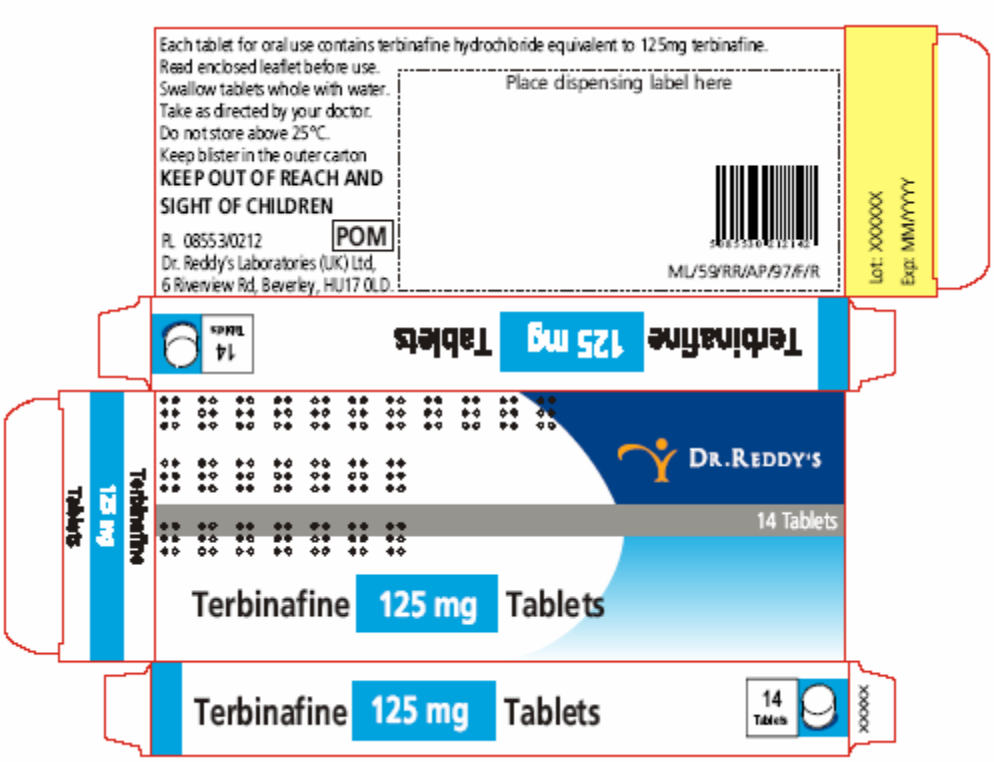
Date of preparation: April 2005
Terbinafine 125mg Tablets PL 08553/0212
Terbinafine 250mg Tablets PL 08553/0213

Component code

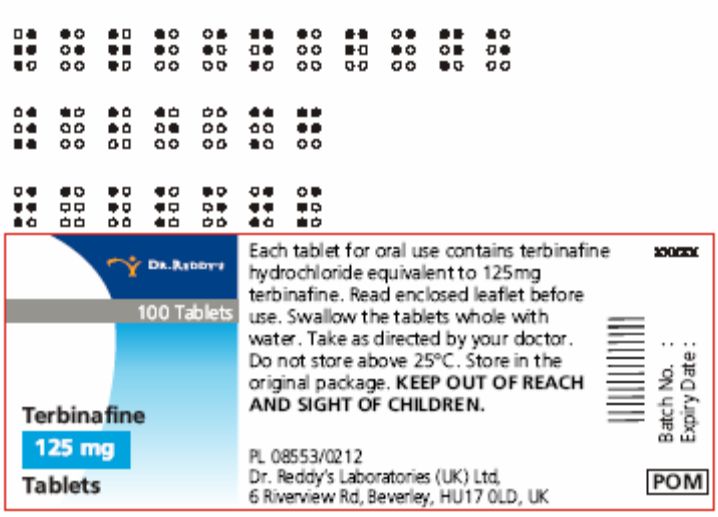
TERBINAFINE 125MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0212

LABELLING

CARTON



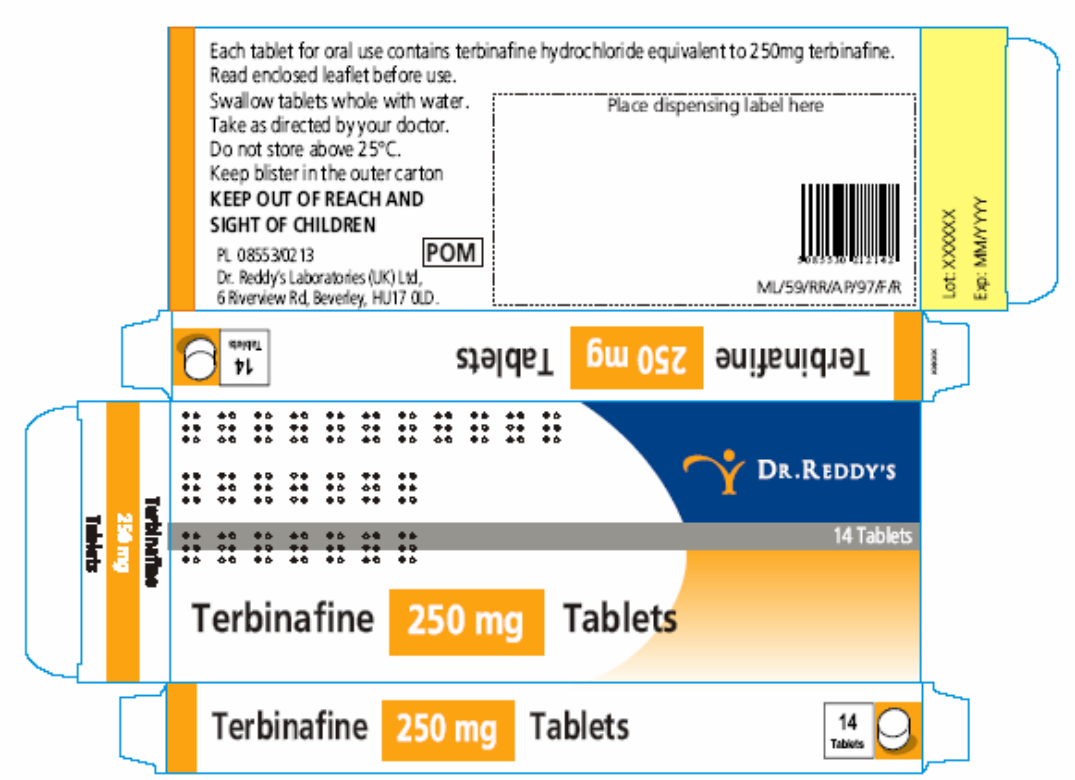
CONTAINER



TERBINAFINE 250MG TABLETS (TERBINAFINE HYDROCHLORIDE)
PL 08553/0213

LABELLING

CARTON



CONTAINER