TERBINAFINE 250MG TABLETS
PL 15922/0037

UKPAR

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TERBINAFINE 250MG TABLETS
PL 15922/0037

LAY SUMMARY

The MHRA today granted Apotex Europe Limited a licence for the medicinal products Terbinafine 250mg Tablets (PL 15922/0037). This is a prescription-only medicine (POM) for the treatment of fungal infections of the skin and nails.

Terbinafine 250mg Tablets contain the active ingredient terbinafine, which is an antifungal drug of the allylamine type. It stops or slows fungal cell wall growth, causing the contents of the cell to be unprotected and eventually die.

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

TERBINAFINE 250MG TABLETS
PL 15922/0037

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Terbinafine 250mg Tablets to Apotex Europe Limited (PL 15922/0037) on 16th January 2007. The product is a prescription-only medicine.

The application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to the original product Lamisil 250mg Tablets (Novartis Pharmaceuticals Limited) which has been authorised in the EU for more than 10 years.

The product contains the active ingredient terbinafine and is indicated for the treatment of fungal infections of the skin and nails caused by Trichophyton (e.g. *T. rubrum, T.mentagrophytes, T. verrucosum, T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum*. Oral terbinafine is indicated in the treatment of ringworm (tinea corporis, tinea cruris and tinea pedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection and the treatment of onychomycosis.

Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that is part of the fungal cell wall synthesis pathway.

PHARMACEUTICAL ASSESSMENT

Active substance

INN: Terbinafine hydrochloride

Chemical Name: (E)-N-6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-I-naphthalene methanamine hydrochloride

Molecular Formula: $C_{21}H_{25}N.HC1$

Molecular Weight: 327.89

Appearance: White to off-white powder

Terbinafine is freely soluble in methanol and methylene chloride, soluble in ethanol and slightly soluble in water. Terbinafine is a non-pharmacopoeial substance.

Terbinafine contains a double bond having the E (trans) geometry. There are no chiral centres in the molecule.

An appropriate method of manufacture of terbinafine hydrochloride has been provided. Appropriate in-process controls are in place to ensure consistency between batches.

An appropriate specification is provided by the active substance manufacturer for terbinafine hydrochloride. The analytical methods provided are suitable and satisfactory validation data have been provided. All reference standards used have been sufficiently characterised and certificates of analysis provided. Batch analysis data have been provided for three batches of active terbinafine and show compliance with the active substance specification.

Satisfactory specifications have been provided for all packaging components.

Appropriate stability data have been provided to support a re-test period of 3 years when stored at room temperature (25 °C). A commitment has been provided to test one batch per year under long-term conditions as part of an ongoing stability programme.

Other ingredients

Other ingredients consist of methylcellulose, croscarmellose sodium, magnesium stearate and colloidal anhydrous silica. All excipients comply with their respective Ph Eur monographs and satisfactory certificates of analysis have been provided.

Magnesium stearate is the only ingredient that comes from an animal source (it is derived from bovine source). An appropriate certificate of suitability for TSE has been provided for magnesium stearate.

Container-closure system

The product is packaged in PVC/PVDC/aluminium blister packs in sizes of 2, 4, 8, 14, 28, 30, 56, 60, 70, 84, 90 and 96 tablets or HDPE bottles with PP caps in pack

sizes of 30 and 120 tablets. Suitable specifications and certificates of analysis have been provided for the finished packaging. All packaging components comply with relevant Ph Eur monographs and guidelines concerning contact with foodstuff.

Product development
A satisfactory pharmaceutical development section has been provided. The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative dissolution profiles have been provided for Lamisil sourced from many EU countries and the proposed product. Impurity profiles for the proposed product and the reference product (UK Lamisil tablets) have also been shown to be comparable.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished product specification
The tablets are white, round and biconvex with bevelled edges, engraved 'APO' on one side and 'TER/250' with a score line on the other side.

The finished product specifications proposed for both release and shelf life are acceptable and provide an assurance of the quality and consistency of the finished product. The analytical methods used have been suitably validated. Batch analysis data has demonstrated compliance with the proposed release specification.

Stability of the product
Stability studies have been provided for batches stored at 25 ºC/60% RH for up to 36 months, 30 ºC/60% RH for 48 weeks and 40 ºC/75% RH for 24 weeks. All batches were stored in the packaging proposed for marketing.

Based on these stability studies, a shelf-life of 2 years has been proposed with storage conditions of "Store in original package" and "Do not store above 25 ºC". These are acceptable.

The applicant has committed to putting the first three commercial batches on long-term stability studies in accordance with the stability protocol used for previous batches and that any of out-of-specification results will be provided to the competent authority.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable.

CONCLUSION
It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Lamisil 250mg Tablets (Novartis Pharmaceuticals Limited), which have been licensed within the EEA for over 10 years.

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption and distribution

Terbinafine is absorbed well orally and in healthy subjects, the C_{max} of 0.86-1.34mg/L is achieved after ~2 hours of a single 250mg oral tablet. There is 70% bioavailability and, although food delays the absorption and t_{max} (from 1.92 to 2.84 hrs), the bioavailability is unaffected. It exhibits dose-proportional linear pharmacokinetics between 125-750mg doses and steady-state plasma concentrations are achieved after 10-14 days in healthy volunteers with 125 or 250mg daily doses.

Terbinafine has a large volume of distribution (range 947.5-2000L with single 250mg dose) and this along with the lipophilic nature, are important for the therapeutic use. It is also highly plasma protein bound (>95%). Expectedly, tissue concentrations are significantly higher than plasma, especially skin (stratum corneum) and nails.

Metabolism and elimination

Terbinafine is extensively metabolised in the liver (partly first-pass) primarily through oxidation by CYP enzymes. At least seven CYP enzymes (importantly CYP2C9, CYP1A2, CYP3A4, and CYP2C8) are involved and it is a competitive inhibitor of CYP2D6. There are nearly 15 known inactive metabolites and, due to the multiplicity of metabolic pathways, there is little interaction or accumulation potential.

Special populations

The important special populations in the context of long-term therapy for nail infections are pregnancy, liver disease and renal failure. Additionally, as terbinafine is extensively metabolised by the liver, liver disease is of greater importance. In all three situations, the brand leader (Lamisil) SmPC states that terbinafine use is not recommended, as there are insufficient data.

The current proposed SmPC is similar to the brand leader SmPC and terbinafine has been contraindicated for patients with liver dysfunction.

Terbinafine should not be used in pregnancy, as nail and ringworm infections even in pregnant women are rarely life-threatening.

Interactions

Terbinafine could be expected to have significant interactions because of its inhibitory effect on CYP2D6. However, because of the multiplicity of enzymatic pathways involved, it has far fewer interactions than other antimycotics.

Important interactions include those with tricyclic antidepressants (nortriptyline, desipramine, and imipramine). Cyclosporin metabolism is accelerated by terbinafine, but in a clinically non-significant fashion. These are highlighted in the SmPC.

Assessor's overall conclusions on pharmacokinetics

The metabolic profile of terbinafine is beneficial to the clinical therapeutic use. Suitable notes have been made in the SmPC for special populations, especially

pregnancy and liver disease. The additional information available about interaction with tricyclic compounds and cyclosporin has been included in the SmPC.

Pharmacodynamics

Mechanism of action

Terbinafine blocks ergosterol biosynthesis in the fungal cell wall, inhibiting enzyme squalene epoxidase which leads to toxic accumulation of Squalene. Terbinafine has very low affinity to mammalian cells in comparison to fungal cells, although the ergosterol synthesis is similar to cholesterol synthesis.

The inner- and outer-arthroconidial membranes are the initial targets of action, followed by cytosol and intracellular organelles. The mean MIC and the mean minimal fungicidal concentration (MFC) for terbinafine in 39 dermatophyte isolates is 0.004 μg/ml, a value much lower than other antifungal agents (e.g. itraconazole MIC 0.078 and MFC 0.595 μg/ml). In contrast to ketoconazole, terbinafine has very little effect on mammalian steroid hormone synthesis.

Genetic differences in pharmacodynamic response

In spite of the multiplicity of metabolic enzymatic pathways involved, no specific genetic polymorphism that affects terbinafine kinetics or pharmacodynamics has been identified so far.

Assessor's overall conclusions on pharmacodynamics

The expert report deals with the pharmacodynamic effects of terbinafine reasonably and the list of fungal organisms is discussed. These are adequately expressed in Section 5.1 of the proposed SmPC. There are no new dynamic data in this application based on essential similarity and this is acceptable.

Bioavailability and Bioequivalence

Bioavailability

The bioavailability of terbinafine is 70% after a single dose of 250mg and is unaffected by food, although the t_{max} is increased. The applicant has not studied bioavailability specifically in this application. The bioequivalence study is discussed below.

Bioequivalence study

In accordance to the regulations on essentially similar products, the applicant has provided a bioequivalence study. The salient features are summarised below. The expert report discusses the study in sufficient detail, but in a non-critical fashion.

Methodology	Randomised, open-label, two-way cross-over study
Reference Product	Lamisil 250mg (Novartis, France;)
Test Formulations	Apotex Terbinafine 250mg
Subjects	24 healthy male volunteers, aged between 18-55 years
Study interval	6 weeks between two periods.

Results:
These are for raw (non-transformed) data and geometric means.

Parameter	Test Prod Apotex Terbinafine 250 Lot No: T1021	Reference Prod Lamisil 250 Lot No: GC9797A	90% CI Point Est (Range)
C_{max} (ng/ml)	1092± 383	1048 ±414	106.4 (93.7-120.7)
$AUC_{(0-t)}$ µg*h/ml	5625 ± 1568	5412 ± 1656	105.0 (96.7-114.0)
$AUC_{(0-\infty)}$ µg*h/ml	6034 ± 1758	5851 ±1832	104.2 (95.9-113.3)
t_{max} (hrs)	1.92 ± 1.02	1.88 ± 0.79	
λ (hr)	0.0226 ± 0.0047	0.0215 ± 0.0038	
$t_{1/2}$ (hr)	32.2 ± 7.5	33.5 ± 7.7	

Assessor's Comments:
Based on the above data from the BE study, the expert concluded that the two products are bioequivalent. The washout period of 6 weeks is appropriate because of the long half-life and lipophilicity of the product, terbinafine. The assessor concurs that the results provided suggest that the two products may be considered bioequivalent.

In response to a question raised during the national assessment, log-transformed data were provided that concur with the results above and show bioequivalence between the test and reference products.

CLINICAL EFFICACY

In this application claiming essential similarity, no new clinical efficacy or safety data have been included. None are necessary, in accordance with the regulations. This is, therefore, acceptable and this aspect is not dealt in detail.

The expert report examines the available literature for use of terbinafine in various mycoses, both superficial and systemic. The indications sought, however, are only for skin and nail infections.

CLINICAL SAFETY

The applicant is not required to submit any new safety data in an application based on essential similarity, and none have been submitted. The expert report examines the clinical safety issue in its body and this is acceptable. There were no major adverse events during the bioequivalence study and only minor events were reported in the 21 patients who completed the study.

Suitable post approval commitments have been made for collecting data and reporting of adverse events, particularly for hepatic dysfunction, and interactions with cylosporin or tricyclic antidepressant medications.

Assessor's overall conclusions on clinical safety:
It is considered that safety profile for terbinafine is acceptable as demonstrated with the reference compound (literature and post marketing surveillance data) and as the current product is bioequivalent with the reference product, the safety profile is acceptable by inference.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medic. The report is fairly detailed examining the potential uses of terbinafine in various fungal infections. The report examines the efficacy and safety issues supporting the acceptable risk-benefit ratio. However, this is a non-critical document that is only modestly helpful at best.

PRODUCT LITERATURE

Summary of Product Characteristics (SPC)

The SPC is satisfactory and consistent with that for the reference product, where appropriate.

Patient Information Leaflet (PIL)

The PIL is satisfactory and consistent with that for the reference product, where appropriate.

Labels

The labels are appropriate for a product of this nature.

CONCLUSIONS

The safety and efficacy of terbinafine have been well-established. The applicant has demonstrated bioequivalence for this product with the reference product (Lamisil) in an appropriately conducted study.

The grant of a marketing authorisation is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Terbinafine 250mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Terbinafine 250mg Tablets and Lamisil 250mg Tablets (Novartis, France).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Terbinafine 250mg Tablets.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. 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 250MG TABLETS
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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 9th December 2002
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 23rd January 2003
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 20th March 2003 and 1st December 2003 and further information relating to the quality dossiers on 23rd April 2003, 7th July 2006 and 27th September 2006.
4	The applicant responded to the MHRA's requests, providing further information for the clinical dossier on 9th June 2003 and 13th June 2005 and further information for the quality dossier on 9th June 2005, 13th September 2006 and 6th November 2006.
5	The applications were determined on 16th January 2007

TERBINAFINE 250MG TABLETS
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Terbinafine 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 281.3 mg terbinafine hydrochloride, equivalent to 250 mg terbinafine.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
The tablets are white, round and biconvex with bevelled edges, engraved 'APO' on one side and 'TER/250' with a score line on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fungal infections of the skin and nails caused by Trichophyton (e.g. *T. rubrum, T.mentagrophytes, T. verrucosum, T. violaceum*), *Microsporum canis* and *Epidermophyton floccosum.*

1. Oral terbinafine is indicated in the treatment of ringworm (tinea corporis, tinea cruris and tinea pedis) where oral therapy is considered appropriate due to the site, severity or extent of the infection.

2. Oral terbinafine is indicated in the treatment of onychomycosis.

Consideration should be given to official guidance on the appropriate use of antifungal agents.

4.2 Posology and method of administration

Adults
250 mg once daily.

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

Skin infections
Likely durations of treatment are as follows:
Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks
Tinea corporis: 4 weeks
Tinea cruris: 2 to 4 weeks

Onychomycosis
The duration of treatment for most patients is between 6 weeks and 3 months. Treatment periods of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of the big toe, or patients of younger age. In the treatment of toenail infections, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer. Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required.

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

Children
A review of safety experience with oral terbinafine in children, which included 314 patients involved in the UK innovator terbinafine tablet, Lamisil™, Post Marketing Surveillance study, has shown that the adverse event profile in children is similar to that seen in adults. No evidence of any new, unusual or more severe reactions to those seen in the adult population have been noted. However, Terbinafine is not recommended for use in children as data is still limited.

Use in the elderly
There is no evidence to suggest that elderly patients require different dosages or experience side-effects different to those of younger patients. The possibility of impairment of liver or kidney function should be considered in this age group (see Precautions).

Use in hepatic impairment
Liver function tests should be performed in all patients before starting oral treatment. Terbinafine should be discontinued if clinical or biochemical evidence of hepatotoxicity develops.

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

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

Method of administration
Via the oral route

4.3 Contraindications
Hypersensitivity to the active substance(s) or to any of the excipients.

4.4 Special warnings and precautions for use
Liver disease
Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within two months of starting treatment. If a patient presents with signs or symptoms suggestive of liver dysfunction such as pruritis, unexplained persistent nausea, anorexia or tiredness, or jaundice, vomiting, fatigue, abdominal pain or dark urine, or pale stools, hepatic origin should be verified and treatment with terbinafine should be discontinued (see 4.8 Undesirable effects). Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine may be reduced by about 50%.

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

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

4.5 Interaction with other medicinal products and other forms of interaction
The plasma clearance of terbinafine may be accelerated by drugs which induce metabolism (such as rifampicin) and may be inhibited by drugs which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such agents is necessary, the dosage of terbinafine may need to be adjusted accordingly. In vitro studies have shown, that terbinafine inhibits the CYP2D6-mediated metabolism. This in vitro finding may be of clinical relevance for patients receiving compounds predominantly metabolised by this enzyme, such as tricyclic antidepressants (TCA's), B-blockers, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAO-Is) Type B. Terbinafine can increase serum levels of imipramine and nortriptyline.

Other studies undertaken in vitro and in healthy volunteers suggest that terbinafine shows very low potential to inhibit or induce the clearance of drugs that are metabolised via other cytochrome P450 enzymes (e.g. cyclosporin, tolbutamine, terfenadine, triazolam, oral contraceptives). Terbinafine is reported not to interact to a clinically relevant extent with cyclosporin, astemizole, cimetidine, midazolam, nifedipine, oral contraceptives, ranitidine, terfenadine, tolbutamide or triazolam.

However, some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) have been reported in patients taking terbinafine concomitantly with oral contraceptives.

4.6 Pregnancy and lactation

Foetal toxicity and fertility studies in animals indicate no adverse effects of Terbinafine on pregnancy or on the health of the foetus/new born child. There is no clinical experience with terbinafine in pregnant women, therefore, unless the potential benefits outweigh any potential risks, terbinafine should not be administered during pregnancy.

Terbinafine is excreted in breast milk and therefore mothers should not receive treatment with terbinafine whilst breast-feeding. Alternatively, breast feeding should be discontinued during treatment with terbinafine.

4.7 Effects on ability to drive and use machines

Terbinafine 250 mg Tablets has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Side effects with Terbinafine are generally mild to moderate, and transient.

The adverse reactions listed below have been classed according to organ, system and frequency. Frequency has been defined as follows: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports. Common and uncommon reactions were determined, in general, on the basis of a series of safety data from the clinical trials population of patients treated with terbinafine and quoted as incidence over and above placebo. Rare and very rare reactions were determined, in general, from post-marketing data and refer to the notification rate rather than the actual frequency.

Blood and the lymphatic system disorders
Very rare: Haematological disorders such as neutropenia, thrombocytopenia and agranulocytosis

Immune system disorders
Common: allergic skin reactions (rash, urticaria)
Very rare: angioneurotic oedema, bronchospasm

Endocrine disorders
Rare: alopecia

Metabolism and nutrition disorders
Common: loss of appetite

Psychiatric disorders
Very rare: depression and anxiety
Nervous system disorders
Common: headache
Rare: dizziness

Ear and labyrinth disorders
Very rare: vertigo

Gastrointestinal disorders
Common: dyspepsia, fullness, nausea, mild abdominal pain, diarrhoea

Hepatobiliary disorders
Rare: cases of serious hepatic dysfunction, including jaundice, cholestasis and hepatitis have been reported. If hepatic dysfunction develops, treatment with terbinafine should be discontinued (see also Precautions). Histological changes due to terbinafine hepatotoxicity may potentially be confused with acute cellular rejection in liver transplant patients taking terbinafine.

Skin and subcutaneous tissue disorders
Very Rare: cases of serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, severe urticaria, photosensitivity, exacerbation of psoriasis) have been reported. If progressive skin rash occurs, treatment with terbinafine should be discontinued. Cutaneous lupus erythematosus induced or exacerbated by terbinafine have been reported. It is to be noted that most of the patients who developed serious skin reactions had a history of autoimmune disease and it has been suggested that this could be a risk factor for developing severe reactions.

Musculoskeletal and connective tissue disorders
Common: arthralgia and myalgia. These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

General disorders and administration site conditions
Uncommon: Taste loss and taste disturbance have been reported in approximately 0.6 % of patients treated with terbinafine; this usually resolves slowly on drug discontinuation.
Rare: Paraesthesia, hypoaesthesia, malaise and fatigue.

4.9 Overdose
A few cases of overdose (up to 5g) 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antifungal for systemic use, ATC code: D01B A02

Terbinafine is an allylamine which has a broad spectrum of antifungal activity. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. The activity versus yeasts is fungicidal or fungistatic depending on the species.

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. Terbinafine does not influence the metabolism of hormones or other drugs.
When given orally, the drug concentrates in skin at levels associated with fungicidal activity.

5.2 Pharmacokinetic properties
A single oral dose of 250 mg terbinafine results in mean peak plasma concentrations of 0.87 mg/l 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. It rapidly diffuses through the dermis and 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 that terbinafine is distributed into the nail plate within the first few weeks of commencing therapy. 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.

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.

The bioavailability of terbinafine is unaffected by food.

5.3 Preclinical 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 dosage 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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methylcellulose
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

PVC/PVDC blister packs of 2, 4, 8, 14, 28, 30, 56, 60, 70, 84, 90 and 96 tablets

Bottles of 30 and 120 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Apotex Europe Limited
41 London Street,
Reading, Berkshire,
RG1 4PS,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 15922/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/01/2007

10 DATE OF REVISION OF THE TEXT
16/01/2007

PATIENT INFORMATION LEAFLET (PIL)

PACKAGE LEAFLET : INFORMATION FOR THE USER

Terbinafine 250 mg Tablets
Terbinafine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Terbinafine 250 mg Tablets is and what it is used for
2. Before you take Terbinafine 250 mg Tablets
3. How to take Terbinafine 250 mg Tablets
4. Possible side effects
5. How to store Terbinafine 250 mg Tablets
6. Further information

1. What Terbinafine 250 mg Tablets is and what it is used for

Terbinafine is an antifungal drug of the allylamine type.

Terbinafine 250 mg Tablets is used to treat patients with fungal infections of the skin and nails. These tablets attack and kill the fungus which is causing your infection.

2. Before you take Terbinafine 250 mg Tablets

Do not take Terbinafine 250 mg Tablets if:
- you are allergic (hypersensitive) to terbinafine or any of the other ingredients of Terbinafine 250 mg Tablets.

If this applies to you, do not take this medicine and talk to your doctor.

Take special care with Terbinafine 250 mg Tablets
Tell your doctor before you start to take this medicine if:
- you are pregnant, or planning to become pregnant. If you do become pregnant whilst taking Terbinafine 250 mg Tablets, tell your doctor.
- you have liver problems or if you have had any disease which may have affected your liver
- you have psoriasis (a disease affecting the skin and joints)
- you have kidney problems

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Some medicines can interfere with your treatment, so make sure to check with your doctor or pharmacist before taking any other medications. In particular, tell your doctor if you are taking any of the following medicines:

- rifampicin
- cimetidine
- oral contraceptives (as irregular periods and breakthrough bleeding may occur in some female patients)
- antidepressants
- beta-blockers used to treat blood pressure and heart conditions.

Taking Terbinafine 250 mg Tablets with food and drink
Taking food and drink has no influence on the treatment with Terbinafine 250 mg Tablets.

Pregnancy and breast-feeding
You should not take Terbinafine 250 mg Tablets if:
- you are pregnant, planning to become pregnant or if you think you may be pregnant
- you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Terbinafine 250 mg Tablets will not affect your ability to drive or operate machinery.

3. How to take Terbinafine 250 mg Tablets

Always take Terbinafine 250 mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow your tablets whole with a glass of water.

The usual dose is 250 mg a day.
- For skin infections Terbinafine is usually taken for between 2 to 6 weeks.
- For nail infections treatment usually lasts between 6 weeks and 3 months, although some patients with toenail infections may need to be treated for 6 months or longer.

If you have the impression that the effect of Terbinafine 250 mg Tablets is too strong or too weak, talk to your doctor.

Patients with kidney problems
Your doctor may prescribe a lower dose.

Children
There are limited data in children and hence Terbinafine is not recommended in children and adolescents under 18 years of age.

If you take more Terbinafine 250 mg Tablets than you should
If you accidentally take too many tablets, tell your doctor **immediately**, or go to your nearest casualty department. If an overdose has been taken there may be signs such as headache, feeling sick, pain in the upper middle region of the abdomen and dizziness.

If you forget to take Terbinafine 250 mg Tablets
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.
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Terbinafine 250 mg Tablets
It is important that you continue taking Terbinafine 250 mg Tablets for as long as your doctor prescribes the medicine. If you stop too soon with the treatment of terbinafine, the symptoms of the disease might come back as seriously as they were before you started the treatment with terbinafine.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Terbinafine 250 mg Tablets can cause side effects, although not everybody gets them.

Common (affecting more than 1 person in 100, but less than 1 in 10)
- allergic skin reactions (rash, urticaria)
- loss of appetite
- headache
- indigestion, fullness, nausea, mild abdominal pain, diarrhoea
- pains in the muscles and joints. These side effects may occur as part of a hypersensitivity (allergic) reaction along with allergic skin reactions (rash, swelling).

Uncommon (affecting more than 1 person in 1,000, but less than 1 in 100)
- taste loss and problems with taste. This usually clears up when you stop taking the medication.

Rare (affecting more than 1 person in 10,000, but less than 1 in 1,000)
- hair loss
- feeling dizzy
- yellowing of your skin or eyes (this may mean you have liver problems). If you notice any of these symptoms stop taking your medication and tell your doctor **immediately**.
- numbness or tingling, hypoaesthesia, feeling unwell, tired.

Very rare (affecting less than 1 person in 10,000, including isolated reports)
- decrease in the number of some blood cells
- swelling of the skin and tissues (angioneurotic oedema), difficulty in breathing or wheezing (bronchospasm)
- depression and anxiety
- a feeling of dizziness or spinning (vertigo)
- severe skin reactions including Stevens-Johnson syndrome (severe allergic reaction that can result in skin blistering, fever and eye damage), toxic epidermal necrolysis (skin becomes intensely red and peels off, often accompanied by blisters), erythema multiforme, severe hives (urticaria), sensitivity to light, or a worsening of psoriasis symptoms. If you notice severe skin rash (swelling, blistering or wheals) stop taking your medication and tell your doctor **immediately**.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Terbinafine 250 mg Tablets

- Keep out of the reach and sight of children.
- Do not store above 25°C.
- Store the tablets in the original package. Only remove them when it is time to take your medicine.

Use-by date
Do not use Terbinafine 250 mg Tablets after the expiry date which is stated on the carton, blister and bottle after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Terbinafine 250 mg Tablets contains
The active substance is terbinafine. Each tablet contains terbinafine hydrochloride equivalent to 250 mg terbinafine.
The other ingredients are methylcellulose, croscarmellose sodium, magnesium stearate, colloidal anhydrous silica.

What Terbinafine 250 mg Tablets looks like and contents of the pack
Terbinafine 250 mg Tablets are white, round and biconvex with bevelled edges, engraved "APO" on one side and "TER/250" with a score line on the other side.
The tablets are available in PVC/PVDC blister packs of 2, 4, 8, 14, 28, 30, 56, 60, 70, 84, 90 and 96 tablets and bottles of 30 and 120 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
Apotex Europe Limited, 41 London Street, Reading, Berkshire, RG1 4PS, United Kingdom

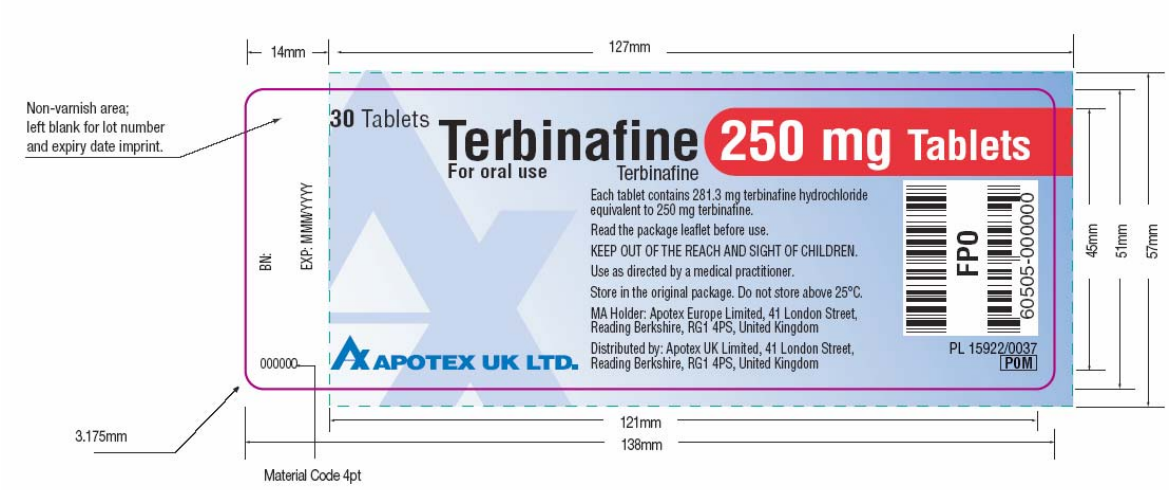
Manufacturer:
Katwijk Farma BV, Archimedesweg 2, 2333 CN, Leiden, The Netherlands

Distributor:
Apotex UK Limited, Rowan House, 41 London Street, Reading, Berkshire, RG1 4PS, United Kingdom

Terbinafine 250 mg tablets: PL 15922/0037

This leaflet was last approved in January 2007.

PACKAGING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30 Tablets
Terbinafine
For oral use
Terbinafine
250 mg Tablets
Each tablet contains 281.3 mg terbinafine hydrochloride equivalent to 250 mg terbinafine.
Read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Use as directed by a medical practitioner.
Store in the original package. Do not store above 25°C.
MA Holder: Apotex Europe Limited, 41 London Street, Reading Berkshire, RG1 4PS, United Kingdom
Distributed by: Apotex UK Limited, 41 London Street, Reading Berkshire, RG1 4PS, United Kingdom
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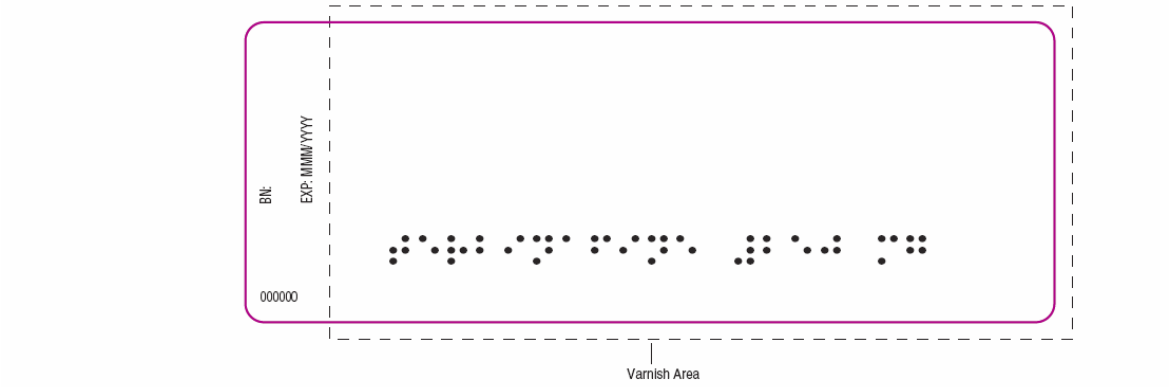
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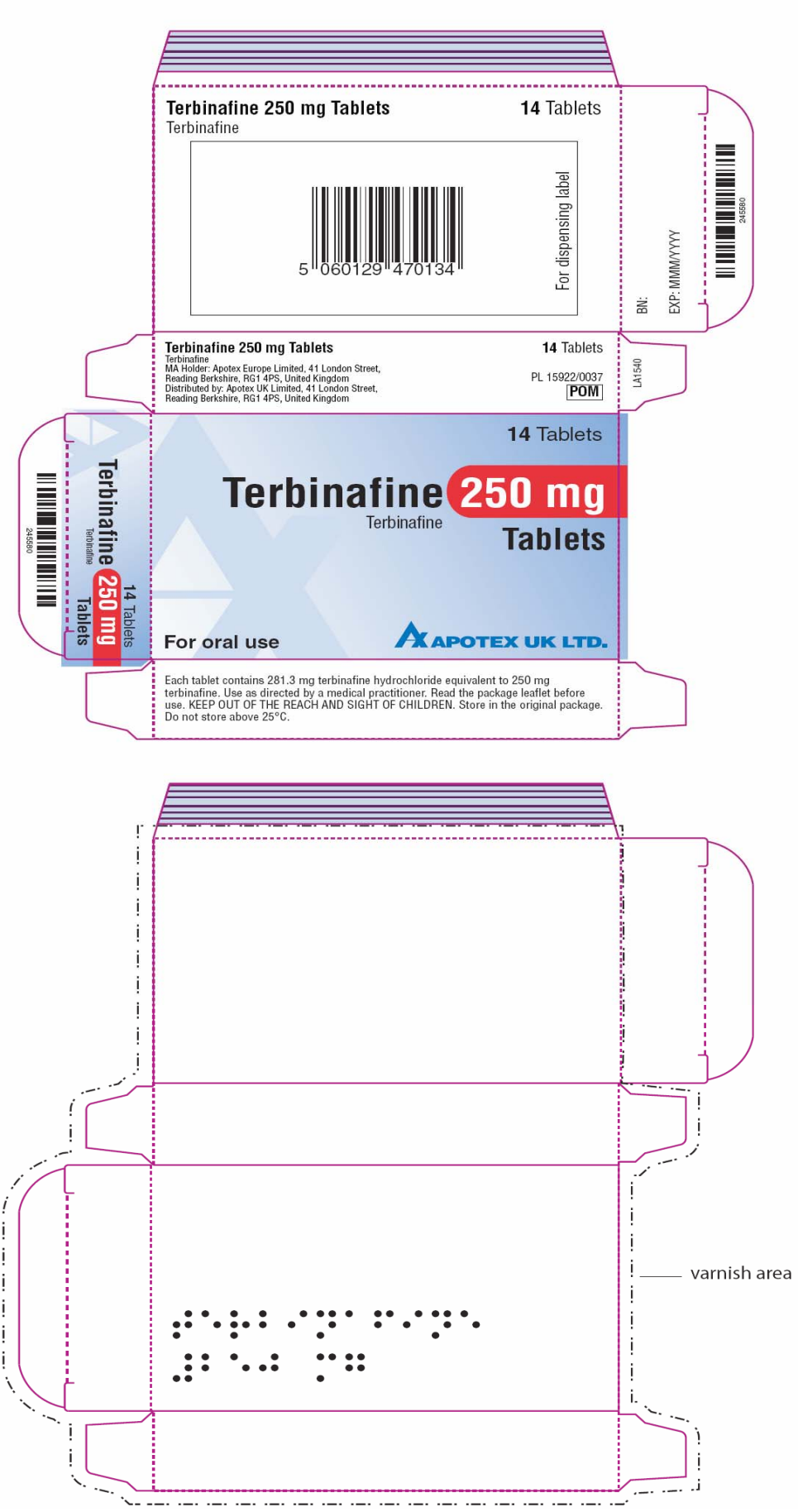
Terbinafine 250 mg Tablets
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Terbinafine 250 mg Tablets
Terbinafine
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Distributed by: Apotex UK Limited, 41 London Street, Reading Berkshire, RG1 4PS, United Kingdom
14 Tablets
PL 15922/0037
POM
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14 Tablets
Terbinafine 250 mg Tablets
Terbinafine
For oral use
APOTEX UK LTD.
Each tablet contains 281.3 mg terbinafine hydrochloride equivalent to 250 mg terbinafine. Use as directed by a medical practitioner. Read the package leaflet before use. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Store in the original package. Do not store above 25°C.
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