Terbinafine 250 mg Tablets
(terbinafine hydrochloride)
PL 33410/0037

UKPAR

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Terbinafine 250 mg Tablets
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LAY SUMMARY

On 30th August 2011, the MHRA granted APSLA Limited a Marketing Authorisation (licence) for the medicinal product, Terbinafine 250 mg Tablets (PL 33410/0037). This is a prescription-only medicine (POM).

Terbinafine 250 mg Tablets contain the active ingredient, terbinafine, which belongs to a group of medicines called antifungals. The tablets are used to treat patients with fungal infections of the skin and nails. Terbinafine attacks and kills the fungus that is causing the infection.

The proposed product was considered to be a generic version of the reference product Lamisil 250 mg Tablets (PL 00101/0304; Novartis Pharmaceuticals UK Limited) based on the data submitted by APSLA Limited.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of Terbinafine 250 mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
Terbinafine 250 mg Tablets
(terbinafine hydrochloride)
PL 33410/0037

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted APSLA Limited a Marketing Authorisation for the medicinal product, Terbinafine 250 mg Tablets (PL 33410/0037) on 30th August 2011. The product is a prescription-only medicine (POM).

This is a generic application for Terbinafine 250 mg Tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The application refers to the UK innovator product, Lamisil 250 mg Tablets (PL 00101/0304), authorised to Novartis Pharmaceuticals UK Limited on 3rd October 1990. The reference product has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Terbinafine 250 mg Tablets are indicated in the treatment of a variety 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*. This includes the following:

- 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.
- Treatment of onychomycosis.

Terbinafine is an allylamine (ATC code - D01BA02) 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. When given orally, the drug concentrates in skin at levels associated with fungicidal activity.

No new non-clinical or clinical efficacy studies were conducted, which is acceptable given that the application was for a generic version of a product that has been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Terbinafine 250 mg Tablets, to that of the reference product, Lamisil 250 mg Tablets (PL 00101/0304, Novartis Pharmaceuticals UK Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.
The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. Routine pharmacovigilance activities according to Volume 9A of the rules governing medicinal products in the EU will be undertaken whilst the product is on the market; this is considered satisfactory. The reference product has been in use for many years and the safety profile of the active is well-established. The excipients used in the medicinal product are well-established and meet EU quality requirements.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). Terbinafine is a well-established active substance that has had widespread clinical use for many years. This was an application for a generic product, which will not be administered at a higher dosage, for a longer duration or for different indications than were previously authorised. There is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the product.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Terbinafine hydrochloride

Nomenclature:

INN: Terbinafine hydrochloride

Chemical name: (2E)-N,6,6-Trimethyl-N-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine hydrochloride

Structure:

\[
\text{Structure Image}
\]

Molecular formula: \( \text{C}_{21}\text{H}_{25}\text{N} \cdot \text{HCl} \)
Molecular weight: 327.9 g/mol
CAS No: 78628-80-5
Physical form: White to off-white powder
Solubility: Very slightly or slightly soluble in water, freely soluble in anhydrous ethanol and in methanol, slightly soluble in acetone

The active substance, terbinafine hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of terbinafine hydrochloride are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). The certificate is accepted as confirmation of the suitability of terbinafine hydrochloride for inclusion in this medicinal product.
MEDICINAL PRODUCT

Description & Composition

Terbinafine 250 mg Tablets are presented as white, circular, biconvex, tablets with ‘TF’ embossed on one side and deep-scored on the other side. Each tablet contains 281.25 mg of terbinafine hydrochloride equivalent to 250 mg of terbinafine.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, sodium starch glycolate, hypromellose, colloidal anhydrous silica and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate has been confirmed as being of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The aim was to develop a stable, immediate-release, generic, tablet formulation containing 250 mg of terbinafine hydrochloride that is bioequivalent to the reference product, Lamisil 250 mg Tablets (PL 00101/0304; Novartis Pharmaceuticals UK Limited).

Comparative dissolution and impurity data were provided for batches of the test and reference products. The dissolution and impurity profiles were satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the manufacturing process. Process validation studies were conducted on pilot-scale batches and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for all reference standards used.
Container Closure System
Terbinafine 250 mg Tablets are licensed for marketing in polyvinylchloride (PVC) -
aluminium foil blister strips, which are placed with the Patient Information Leaflet
(PIL) into cardboard outer cartons in pack sizes of 14 or 28 tablets. The MAH has
stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components
used have been provided. All primary product packaging complies with EU
legislation, Directive 2002/72/EC (as amended), and is suitable for contact with
foodstuffs.

Stability
Finished product stability studies have been conducted in accordance with current
guidelines, using product stored in the packaging proposed for marketing. These data
support the applied shelf-life of 3 years, with the storage instructions ‘Store below
25°C. Keep the blisters in the outer carton in order to protect from light’.

Quality Overall Summary
A satisfactory quality overview is provided, and has been prepared by an
appropriately qualified expert. The CV of the expert has been supplied.

Product Information
The approved Summary of Product Characteristics (SmPC), Patient Information
Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have
been provided. The PIL user-testing report has been evaluated and is accepted. The
labelling fulfils the statutory requirements for Braille.

Conclusion
The quality grounds for these applications are considered adequate. There are no
objections to approval of Terbinafine 250 mg Tablets from a pharmaceutical point of
view.
NON-CLINICAL ASSESSMENT

This abridged application, submitted under Article 10(1) of Directive 2001/83/EC, as amended, is for Terbinafine 250 mg Tablets, claiming to be a generic product of Lamisil 250 mg Tablets (PL 00101/0304; Novartis Pharmaceuticals UK Limited).

No new non-clinical data have been supplied with this application and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the expert has been supplied.

The MAH has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).

There are no objections to approval of this product from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL BACKGROUND

Terbinafine is an orally and topically active allylamine antifungal agent with a primarily fungicidal action in vitro. Its spectrum of in vitro activity includes a broad range of dermatophyte, filamentous, dimorphic and dematiaceous fungi, and some yeast species. In clinical trials, mycological cure and overall efficacy rates of around 90% and 80%, respectively, have been achieved in cutaneous dermatophyte infections (tinea corporis/cruris and tinea pedis) with terbinafine, administered either orally (250 or 500 mg/day) or topically (a 1% cream applied twice daily). Similar rates of cure have been obtained with oral terbinafine in dermatophyte nail infections after relatively short treatment periods ranging from 3 to 12 months. Oral terbinafine appeared to be at least as effective as oral griseofulvin or ketoconazole in tinea corporis/cruris and more effective than griseofulvin in tinea pedis. Both oral and topical terbinafine have been very well tolerated in clinical trials to date, with only minor adverse effects.

INDICATIONS

Terbinafine 250 mg Tablets are indicated in the treatment of a variety of fungal infections of the skin and nails caused by Trichophyton (eg. T. rubrum, T. mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum. This includes the following:

- 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.
- Treatment of onychomycosis.

The indications are consistent with those for the UK reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the UK reference product and is satisfactory.

TOXICOLOGY

The toxicology of terbinafine hydrochloride is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of terbinafine hydrochloride is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for this application.
Pharmacokinetics – bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Terbinafine 250 mg Tablets, to that of the reference product, Lamisil 250 mg Tablets (PL 00101/0304; Novartis Pharmaceuticals UK Limited). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis were provided for both the test and reference products.

This was a randomised, open-label, two-period, two-sequence, two-way crossover, single-dose bioequivalence study conducted in 32 healthy, adult human male subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 14 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 96.0 hours after administration of test or reference product. Plasma levels of terbinafine hydrochloride were quantified by a validated LC-MS/MS bioanalytical method.

The primary pharmacokinetic parameters for this study were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

Results:

32 subjects were enrolled in the study; 31 of these completed the study and the data from 30 subjects were included in the pharmacokinetic evaluation and statistical analysis. The discontinuation and non-inclusion in the pharmacokinetic analysis of two subjects was satisfactorily justified.

Safety – There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Geometric Least Squares Mean</th>
<th>90% CI (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (X)</td>
<td>Test Product (Y)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>1212.91</td>
<td>1273.91</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.h/ml)</td>
<td>7272.20</td>
<td>7264.15</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/ml)</td>
<td>7926.55</td>
<td>7931.36</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ maximum plasma concentration, $AUC_{0-t}$ area under the plasma concentration-time curve from time zero to t hours, $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity.
Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for $C_{\text{max}}$, $\text{AUC}_{0-1}$, and $\text{AUC}_{0-\infty}$ for terbinafine hydrochloride fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

CLINICAL EFFICACY

No new data have been submitted and none are required. The reference product is established and the application depends upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of terbinafine hydrochloride is well-established from its extensive use in clinical practice.

CLINICAL SAFETY

No new safety data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of terbinafine hydrochloride is well-known.

CLINICAL OVERVIEW

A satisfactory clinical overview is provided and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is satisfactory.

Patient Information Leaflet (PIL)

The final PIL is in line with the approved SmPC and is satisfactory. The PIL user-testing has been evaluated and is accepted.

Labelling

The labelling is satisfactory.

CONCLUSION

Sufficient clinical information has been submitted to support this application. The risk-benefit of the product is considered favourable from a clinical perspective. The grant of a Marketing Authorisation was, therefore, recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Terbinafine 250 mg 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Terbinafine 250 mg Tablets and the reference product, Lamisil 250 mg Tablets (PL 00101/0304; Novartis Pharmaceuticals UK Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC is consistent with that of the UK reference product and is satisfactory.

The final PIL is in line with the SmPC and is satisfactory. The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Mock-ups of the labelling have been provided. The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study support the claim that the applicant’s Terbinafine 250 mg Tablets is a generic version of the UK reference product, Lamisil 250 mg Tablets (PL 00101/0304; Novartis Pharmaceuticals UK Limited). Extensive clinical experience with terbinafine hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Terbinafine 250 mg Tablets
(terbinafine hydrochloride)
PL 33410/0037

STEPS TAKEN FOR ASSESSMENT

1  The MHRA received the marketing authorisation application on 18th September 2008.

2  Following standard checks and communication with the applicant the MHRA considered the application valid on 1st October 2008.

3  Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 1st June 2009 and 3rd February 2010; and further information relating to the quality dossier on 22nd September 2009, 23rd March 2010, 8th June 2010 and 29th March 2011.

4  The applicant responded to the MHRA’s requests, providing further information for the clinical sections on 22nd September 2009 and 25th February 2010; and further information for the quality sections on 29th January 2010, 30th May 2010, 7th December 2010 and 7th July 2011.

5  The application was granted on 30th August 2011.
Terbinafine 250 mg Tablets
(terbinafine hydrochloride)
PL 33410/0037

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Terbinafine 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 281.25 mg terbinafine hydrochloride, equivalent to 250 mg terbinafine.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet.
White circular, biconvex, tablets with TF embossed on one side and deep score on the other side.

4 CLINICAL PARTICULARS

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

- 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.
- Treatment of onychomycosis.

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.

Additional information on special population

Liver impairment
Terbinafine tablets are not recommended for patients with chronic or active liver disease (see section 4.4).
Renal impairment

The use of terbinafine tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 and section 5.2).

Children

A review of safety experience with oral terbinafine in children, which includes 314 patients involved in the UK terbinafine 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, as data is still limited its use is not recommended.

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 section 4.4).

Method of administration

Via the oral route.

4.3 Contraindications

Hypersensitivity to terbinafine or to any of the excipients.

4.4 Special warnings and precautions for use

Liver Function

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. 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 liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine tablets was uncertain (see section 4.8).

Patients prescribed terbinafine tablets should be instructed to report immediately any signs or symptoms suggestive of liver dysfunction such as pruritus, unexplained persistent nausea, anorexia or tiredness, or jaundice, vomiting, fatigue, abdominal pain or dark urine, or pale stools. Patients with these symptoms should discontinue taking oral terbinafine and the patient's liver function should be immediately evaluated.

Dermatological effects

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

Haematological effects

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with terbinafine tablets. Aetiology of any blood dyscrasias that occur in patients treated with terbinafine tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with terbinafine tablets.

Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine may be reduced by about 50%.

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

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micro mol/L) the use of terbinafine tablets has not been adequately studied, and therefore, is not recommended (see section 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on terbinafine

The plasma clearance of terbinafine may be accelerated by drugs which induce metabolism and may be inhibited by drugs which inhibit cytochrome P450. Where coadministration of such agents is necessary, the dosage of terbinafine may need to be adjusted accordingly.

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

Cimetidine decreased the clearance of terbinafine by 30%.

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

Rifampicin increased the clearance of terbinafine by 100%.

Effect of terbinafine on other medicinal products

Studies undertaken in vitro and in healthy volunteers suggest that terbinafine shows negligible potential to inhibit or induce the clearance of drugs that are metabolised via other cytochrome P450 enzymes (e.g. tolbutamine, terfenadine, triazolam, oral contraceptives) with exception of those metabolised through CYP2D6 (see below).

Terbinafine does not interfere with the clearance of antipyrine or digoxin.

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

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

Caffeine – Terbinafine decreased the clearance of caffeine administered intravenously by 21%. Compounds predominantly metabolised by CYP2D6 – In vitro and in vivo studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for patients receiving compounds predominantly metabolised by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCA’s), β-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B.

Terbinafine decreased the clearance of desipramine by 82%.

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

Terbinafine increased the clearance of ciclosporin by 15%.

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

4.6 Fertility, Pregnancy and Lactation

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

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 terbinafine treatment whilst breast-feeding.
4.7 Effects on ability to drive and use machines

No studies on the effects of terbinafine tablets treatment on the ability to drive and use machines have been performed. Patients who experience dizziness as an undesirable effect should avoid driving vehicles or using machines.

4.8 Undesirable effects

Side effects are generally mild to moderate, and transient. The following adverse reactions have been observed in the clinical trials or during post-marketing experience.

Adverse reactions are ranked under headings of frequency, using the following convention:

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.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very rare</th>
<th>Neutropenia, agranulocytosis, thrombocytopenia.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not known</td>
<td>Pancytopenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Very rare</td>
<td>Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very rare</td>
<td>Psychiatric disturbances (such as depression and anxiety)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Taste disturbances, including taste loss, which usually recover slowly after discontinuation of the drug. Very rare cases of prolonged taste disturbance have been reported, sometimes leading to a decrease of food intake and significant weight loss.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Paraesthesia, hypoesthesia, dizziness</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Very rare</td>
<td>Vertigo</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Gastrointestinal symptoms (feeling of fullness, loss of appetite, dyspepsia, nausea, mild abdominal pain, diarrhoea).</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Rare</td>
<td>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). 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 and a causal association with the intake of terbinafine was uncertain.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common</td>
<td>Non-serious forms of skin reactions (rash, urticaria).</td>
</tr>
</tbody>
</table>
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).

Musculoskeletal and connective tissue disorders

Very common  Musculoskeletal reactions (arthralgia, myalgia).

General disorders

Rare  Malaise

Not known  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: Dermatologicals: antifungals for systemic use

ATC code: D01BA02

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.

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 0.97 μg/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. 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 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 69mg/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, 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 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

Microcrystalline cellulose
Sodium starch glycolate (Type A)
Hypromellose (15cP)
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Keep the blisters in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/ Aluminium blister strips containing 14 or 28 tablets in a carton.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3, Ireland
8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/08/2011

10 DATE OF REVISION OF THE TEXT
30/08/2011
UKPAR Terbinafine 250 mg Tablets  
PL 33410/0037

PRODUCT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Terbinafine 250 mg Tablets
(Terbinafine hydrochloride)

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 any further questions, 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 is and what it is used for
2. BEFORE YOU TAKE Terbinafine
3. HOW to take Terbinafine
4. POSSIBLE side effects
5. HOW to store Terbinafine
6. Further information

1. WHAT Terbinafine is and what it is used for

The name of your medicine is Terbinafine. 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.

The active ingredient contained in the tablets is terbinafine. The tablets contain terbinafine hydrochloride equivalent to 250 mg terbinafine.

Terbinafine is used to treat patients with fungal infections of the skin and nails. It attacks and kills the fungus which is causing your infection.

2. BEFORE YOU TAKE Terbinafine

Do not take Terbinafine:
- If you are a child under 12 years of age.
- If you suspect that you have had an allergic reaction to, or have been upset by any of the ingredients in terbinafine (listed in "What Terbinafine contains").
- If you have any liver problems or have had any disease which may have affected your liver.
- If you have glaucoma.
- If you have any kidney problems.
- If you are pregnant, or planning to become pregnant. If you do become pregnant whilst taking Terbinafine, tell your doctor.
- If you are breast feeding.

Terbinafine is not recommended for children.

Taking other medicines

Some medicines can interfere with your treatment, so make sure to check with your doctor or pharmacist before taking any other medicines. In particular, tell your doctor if you are taking any of the following:

- Rifampicin
- Cimetidine
- Oral contraceptives (as irregular periods and breakthrough bleeding may occur in some female patients).
- Antidepressants
- Beta-blockers or anti-arrhythmics for heart problems
- Warfarin, a medicine used to thin your blood
- Medicines to treat heart problems (eg propranolol)
- Ciclosporin, a medicine used to control your body's immune system in order to prevent rejection of transplanted organs
- Carbamazepine

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you go into hospital, let the medical staff know you are taking terbinafine.

Pregnancy and breast-feeding

You should not take terbinafine if you are pregnant or are breast feeding unless your doctor has specifically recommended it. Breast feeding should be discontinued in case you are required to take terbinafine.

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

Driving and using machines

Patients who experience dizziness as an undesirable effect should not drive or operate machinery.

3. HOW TO TAKE Terbinafine

Your doctor will decide the right dose of terbinafine and will tell you how long to take your medicine for. Follow your doctor's instructions exactly and never change the dose yourself. Ask your doctor or pharmacist if you are unsure about how much medicine to take or when to take it.

The usual dose is 256 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.

Do not chew. Swallow your tablets with a glass of water.

XX
If you take more terbinafine than you should, contact your doctor. In the case of an overdose, contact the nearest hospital casualty department immediately.

It is important to take terbinafine as directed by your doctor.

If you forget to take a dose, take it as soon as you remember.

Do not take a double dose to make up for a forgotten dose. If you are worried, ask your doctor or pharmacist for advice.

Do not stop taking your tablets, even if you are feeling well, unless your doctor tells you.

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 tablets may occasionally cause side effects, although not everybody gets them. Side effects are often mild to moderate and may wear off after a while.

**Common side effects:**
- Headache
- Poor appetite or a slight sick feeling
- Indigestion
- Mild abdominal pain or fullness
- Diarrhoea
- Itching, rash or swelling
- Pain in the muscles and joints, which may occur as part of a hypersensitivity (allergic) reaction along with allergic skin reactions (red, swelling).

**Uncommon side effects:**
- Taste loss and taste disturbance (which usually returns to normal within a few weeks of discontinuation of the medication).
  - A very small number of patients have reported prolonged taste disturbance. As a result, in very few severe cases, a reduction in the amount of food eaten has led to significant weight loss.

**Rare side effects:**
- Feeling unwell, tired or dizzy
- Numbness or tingling

If you notice any of the following rare symptoms occurring stop taking your medication and tell your doctor immediately:
- Yellowing of your skin or eyes (this may indicate liver problems)
- Severe skin rash (swelling, blisters or peeling — raised, itchy areas of skin which could be a sign of an allergy)
- Weakness, unusual bleeding, bruising or frequent infections (this may be a sign of blood disorders)

Very rare side effects:
- Feeling tired
- Decrease in the number of some blood cells
- Depression and anxiety
- Worsening of psoriasis symptoms
- Yeast infection

May cause or worsen a condition called lupus (a long-term illness with symptoms including skin rash and pain in the muscles and joints)

The following have also been reported:
- Pica: craving for unusual or harmful substances (such as clay or perlite)
- Signs of blood disorders: weakness, unusual bleeding, bruising or frequent infections.

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

Keep out of the reach and sight of children.

Do not use terbinafine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month. Leave your tablets in the foil. Only remove them when it is time to take your medicine.

Store below 25°C. Keep the blister in the outer carton in order to protect from light.

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 protect the environment.

6. FURTHER INFORMATION

What terbinafine contains
- The active substance is terbinafine. Each tablet contains 250 mg terbinafine (as terbinafine hydrochloride)
- The other ingredients of the tablets are microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, colloidal anhydrous silica, hypromellose (15 SP).

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

What terbinafine looks like and contents of the pack
- Terbinafine 250 mg Tablets are white circular, bi-convex, tablets with TF embossed on one side and deep scores on the other side.
- Terbinafine Tablets are available in packs containing 14 and 28 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
APSLA Limited, Bayview House, 49 North Strand Road, Dublin 3, Ireland.

Manufacturer:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97 – 107 Uxbridge Road, Ealing, London W5 7TL

Distributed by:
APC Pharmaceuticals & Chemicals (Europe) Ltd., 9th floor, C.P. House, 97 – 107 Uxbridge Road, Ealing, London W5 7TL

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For more information on terbinafine or for this leaflet in formats suitable for the blind and partially-sighted, please contact APC Pharmaceuticals & Chemicals (Europe) Ltd, telephone number 0208 326 3220
LABELLING

Carton – pack size 14
Carton – pack size 28
Blister foil

Braille

Terbinfine 250 mg Tablets