Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Terbinafine 250mg Tablets

MRP no: UK/H/805/01
UK licence no: PL 20137/0008

Applicant: Clarendon Pharma Limited

Terbinafine 250mg Tablets

LAY SUMMARY

Belgium, Denmark, Germany, Finland, Italy, Malta, The Netherlands, Norway, Portugal, Slovenia, Slovakia, Poland, Hungary and Czech Republic today granted Clarenden Pharma Limited Marketing Authorisations (licences) for the medicinal product Terbinafine 250mg Tablets (PL 20137/0008). These are prescription-only medicines (POM) for the treatment of severe fungal infections of the skin, including those in between the fingers and toes, and of the nails.

Terbinafine Tablets contain the active ingredient terbinafine, which belongs to a group of drugs called antifungals.

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 Marketing Authorisations have been granted.

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Module 1

Product Name	Terbinafine 250mg Tablets
Type of Application	Abridged Initial application Generic, Article 10.1 [formerly 10.1(a)(iii)] Chemical substance Prescription only
Active Substance	Terbinafine Hydrochloride
Form	Tablets
Strength	250mg
MA Holder	Clarendon Pharma Ltd
RMS	United Kingdom
CMS	Belgium, Denmark, Germany, Finland, Italy, Malta, The Netherlands, Norway, Portugal, Slovenia, Slovakia, Poland, Hungary and Czech Republic.
Procedure Number	UK/H/805/01
Timetable	Day 90 09/05/2006

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Terbinafine 250mg Tablets (UK)
Terbinafine Arrow 250 mg Comprimes (BE)
Terbinafini Arrow (CZ)
Terbinafin Recept Pharma 250 mg Tabletti (FI)
Terbina-Q 250 mg Tabletten (DE)
Terbinafine Arrow 250mg Tabletta (HU)
Terbinafina Arrow 250 mg Compresse (IT)
Terbinafine 250 mg Tablets (MT)
Terbinafine 250 mg Tabletten (NL)
Terbinafin Recept (NO)
Terbinafina 250mg Tabletki (PO)
Terbinafina Arrowblue 250 mg Comprimidos (PT)
Terbinafin Arrow 250mg (SL)
Terbinafin Arrow 250mg tablete (SK)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Tablet

White round tablet, with the letter ‘T’ and scoreline on opposite faces.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Fungal infections of the skin and nails caused by dermatophytes such as Trichophyton (*T. rubrum, T. mentagrophytes, T. verrucosum, T. tonsurans, T. violaceum*), Microsporum canis and Epidermophyton floccosum such as tinea corporis, tinea cruris and tinea pedis, when oral therapy is considered appropriate due to the site, severity or extent of the infection.
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:

The usual dose is 250mg once daily, however, the duration of treatment will vary according to the indication and the severity of the infection.

Skin infections
The most usual duration of treatment is tabulated below:

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 and is only seen several months after stopping treatment which is the time for outgrowth of a healthy nail.

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

Use in the elderly above 65 years of age:
There is no evidence to suggest that elderly patients require a different dosage regimen or experience side-effects different to those of younger patients. The possible impairment of liver or kidney function should be considered in this age group (see Section 4.4).

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

Hepatic insufficiency
Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine may be reduced by about 50%. The therapeutic use of terbinafine in patients with chronic liver disease has not been studied and therefore cannot be recommended

Method of administration
The tablet should be swallowed whole with water with or without food

4.3. Contraindications
Peroral terbinafine is contraindicated in patients with hypersensitivity to terbinafine or to any of the excipients and in patients with severe hepatic impairment.

4.4. Special warning and special precautions for use
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, jaundice, vomiting, fatigue, abdominal pain or dark urine, or pale stools, hepatic origin should be verified and terbinafine therapy should be immediately terminated.

Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that the clearance of terbinafine may be reduced by about 50%. The therapeutic use of terbinafine in patients with chronic or active liver disease has not been studied and therefore cannot be recommended.

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

Orally administered terbinafine is not effective against Pityriasis versicolor and vaginal candidiasis.

Terbinafine should be used with caution in patients with impaired renal function.

Terbinafine can in very rare cases cause liver failure in patients with or without pre-existing liver disease which can lead to liver transplantation or death (hepatotoxicity). It is recommended that serum transaminase levels should be determined before the beginning of therapy which can give indications of an acute or pre-existing liver disease.

If a patient develops a neutropenia/agranulocytosis (symptoms e.g fever, tonsillitis or any other infection) or an extensive cutaneous reaction or one which touches the mucous membrane, therapy should be discontinued.

4.5. Interactions 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 dose 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 (TCAs), *β*-blockers, selective serotonine reuptake inhibitors (SSRIs), the antiarrhythmics mexiletine and propafenone and monoamine oxidase inhibitors (MAO-Is) Type B. These patients should be carefully monitored.

Other 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. ciclosporin, tolbutamide, terfenadine, triazolam, oral contraceptives). 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

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

There are no adequate data from the use of terbinafine in pregnant women, therefore it should not be given during pregnancy unless clearly necessary.

Lactation
Terbinafine is excreted in breast milk and therefore mothers should not receive peroral terbinafine whilst breast-feeding.

4.7. Effects on ability to drive and use machines

Peroral terbinafine has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

	Common >1/100, <1/10	**Uncommon >1/1,000. <1/100**	**Rare >1/10,000, <1/1,000**	**Very rare <1/10,000**
Blood and lymphatic system disorders				**Agranulocytosis, Neutropenia, Thrombocytopenia**
Immune system disorders			**Anaphylactic reaction, Serum sickness like reaction**	**Manifestation or aggravation of cutaneous or systemic lupus erythematosus**
Metabolism and nutrition disorders	**Loss of appetite**			
Psychiatric disorders				**Anxiety, Depression**
Nervous system disorders	**Headache**	**Ageusia, Dysgeusia**	**Dizziness, Hypoaesthesia, Paraesthesia**	
Gastrointestinal disorders	**Abdominal distension, Abdominal pain, Diarrhoea, Dyspepsia, Nausea**			
Hepatobiliary disorders			**Cholestasis,* Hepatic function abnormal,* Hepatitis,* Jaundice***	
Skin and subcutaneous tissue disorders	**Rash, Urticaria**		**Angioneurotic oedema**	**Photosensitivity reaction, Exacerbation of psoriasis, * Stevens-Johnson syndrome, Toxic epidermal necrolysis, Hair loss**
Musculoskeletal and connective	**Arthralgia, Myalgia**			

tissue disorders				
Reproductive system and breast disorders				**Menstruation irregular, Breakthrough bleeding**
General disorders and administration site conditions	**Fatigue, Malaise**			
Investigations			**Hepatic enzyme increased***	

* See section 4.4

4.9. Overdose

A few cases of overdose (up to 5g) have been reported

Symptoms:
Headache, nausea, epigastric pain and dizziness.

Treatment:
The recommended treatment of overdose consists of 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: 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, nails and hair at levels associated with fungicidal activity. It is still present there 15 to 20 days after stopping treatment.

5.2. Pharmacokinetic properties

A single oral dose of 250mg terbinafine results in mean peak plasma concentrations of 0.97µg/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%). 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. Terbinafine is rapidly metabolised by 7 isoenzymes of the CYP-type, mainly 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.

The bioavailability is about 80%, which is only slightly affected by food and therefore a dose adjustment is not necessary.

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 , 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 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

Silica, colloidal anhydrous
Hypromellose
Sodium starch glycollate (Type A)
Magnesium stearate

6.2. Incompatibilities

Not applicable

6.3. Shelf-Life

3 years.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

PVC/PVDC/Aluminum blister pack
Pack sizes: 14 or 28 tablets

6.6. Instruction for use, handling and disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Module 3

Product Information Leaflet

PACKAGE LEAFLET : INFORMATION FOR THE USER

Terbinafine 250mg 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 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 250MG TABLETS ARE AND WHAT THEY ARE USED FOR

Terbinafine 250mg Tablets belong to a family of medicines known as antifungals and can be used for the treatment of severe fungal infections of the skin (including those in between the fingers and toes) and of the nails.

2. BEFORE YOU TAKE TERBINAFINE 250MG TABLETS

Do not take Terbinafine 250mg Tablets if:
- You are allergic (hypersensitive) to terbinafine or any of the other ingredients (these are listed in section 6)
- You have a severe liver problem.

Take special care with Terbinafine 250mg Tablets if:
- You have liver problems or a disease which may affect your liver
- You have psoriasis
- You have kidney problems
- You are pregnant, planning to become pregnant or you are breast-feeding.

If any of the above apply to you, tell your doctor before you start taking this medicine.

Taking other medicines:
Tell your doctor if you are taking any of the following as they may affect the way this medicine or your other medicine works:
- the antibacterial medicine, rifampicin
- the anti-ulcer medicine, cimetidine
- tricyclic antidepressants such as clomipramine or lofepramine
- certain antidepressants called selective serotonin reuptake inhibitors (SSRIs) e.g. paroxetine
- certain medicines called monoamine oxidase inhibitors e.g. selegiline used to treat Parkinson's disease
- beta-blockers such as atenolol or carvedilol
- oral contraceptives ("the pill") as irregular periods or breakthrough bleeding may occur in female patients
- mexiletine and propafenone which are used to treat heart flutters (arrhythmias).

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

Pregnancy and breast-feeding
If you are pregnant, think you are pregnant or are breast-feeding you should not take Terbinafine 250mg Tablets unless your doctor tells you to. If you become pregnant whilst taking this medicine you should tell your doctor as soon as possible.

Ask your doctor for advice before taking any medicine.

Driving and using machines
Terbinafine 250mg Tablets should not affect your ability to drive or use machines.

3. HOW TO TAKE TERBINAFINE 250MG TABLETS

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

Adults
The dose you are prescribed will depend on the type of infection and how bad it is. The usual dose is one tablet daily. You should swallow your tablet whole with a glass of water. The tablets can be taken with or without food.

If you suffer from a kidney problem, your doctor will probably prescribe half the recommended dose.

Duration of treatment
Your doctor will tell you how long your treatment with terbinafine will last.

For general skin infections, your treatment will probably last for 4 weeks.

Treatment for skin infections affecting the genital area will normally last between 2 to 4 weeks and those involving the feet may last between 2 to 6 weeks.

For nail infections your treatment may last between 6 weeks and 3 months, although treatment for toenail infections may continue for 6 months or longer.

Complete resolution of the signs and symptoms of the infection may not occur until several weeks after treatment has stopped and the infection has been cured.

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

If you take more Terbinafine 250mg Tablets than you should, you may feel dizzy, sick and have a headache and/or stomach pain. If you or someone you know has taken more tablets than they should, consult your doctor or the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken.

If you forget to take Terbinafine 250mg Tablets at the right time, take them as soon as you remember. Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

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

If you suffer from any of the following symptoms, stop taking your tablets and tell your doctor **immediately**. If you ignore these symptoms they can lead to more serious problems:

- Unexpected skin reactions, e.g. rash and/or sore or blistering skin, mouth, eyes and/or genitals (including those which may affect large parts or the whole body)
- You get a swollen face, tongue and/or throat, severe reddening of the skin (hives) and/or have difficulty in swallowing and/or breathing (angioedema). This can be a result of an allergic reaction
- If you get a high temperature, "flu like" symptoms or tonsillitis (sore throat)
- There have been reports of abnormalities in liver function. Symptoms of this can include yellowing of the skin, itching, unexplained and persistent nausea (feeling sick), tiredness, vomiting (being sick), dark coloured urine, light coloured stools and abdominal (tummy) pain.

If you are unsure about any of the above, talk to your doctor, who will be able to explain more about what to look for and what to do.

The following side effects have also been reported:

Common (affecting less than 1 in 10 people taking this medicine): loss of appetite, headache, stomach ache or a feeling of fullness, diarrhoea, indigestion, nausea (feeling sick), rash, urticaria (reddening of the skin with itching), joint and/or muscle pain, fatigue and a general feeling of being unwell.

Uncommon (affecting less than 1 in 100 people taking this medicine): Loss of taste and disturbances in taste (this usually resolves once treatment has been stopped).

Rare (affecting less than 1 in every 1,000 people taking this medicine): serious allergic reactions causing rash and localised swelling especially of the face and throat, dizziness, numbness and tingling ("pins and needles"), liver problems including hepatitis (liver inflammation), jaundice (yellowing of the skin and eyes) and increased liver enzymes.

Very rare (affecting less than 1 in 10,000 people taking this medicine): anxiety, depression, hair loss, sensitivity to light, irregular and/or breakthrough bleeding, systemic lupus erythematosus (a condition which causes joint pain, rash and fever), toxic epidermal necrolysis (a serious illness with blistering of the skin), Stevens-Johnson syndrome (a serious illness with blistering of the skin, mouth, eyes and genitals) and certain blood disorders including neutropenia, thrombocytopenia and agranulocytosis (these are reductions in the number of different types of blood cells).

If you already suffer from psoriasis, there is a very rare possibility that it may get worse when you take these tablets.

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

5. HOW TO STORE TERBINAFINE 250MG TABLETS

Keep out of the reach and sight of children.

Do not take Terbinafine 250 mg Tablets after the expiry date which is stated on the blister and carton after EXP:. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

If you have any tablets left after taking all the doses prescribed for you, please return these to your pharmacist.

If you notice any visible signs of deterioration in the tablets, such as chipped, broken or discoloured tablets, take them to your pharmacist for advice before taking them.

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 250mg Tablets contain:

- The active substance is terbinafine (each tablet contains 250mg of terbinafine (as hydrochloride)
- The other ingredients are microcrystalline cellulose, colloidal anhydrous silica, hypromellose, sodium starch glycollate and magnesium stearate.

What Terbinafine 250mg Tablets look like and contents of the pack

Each tablet is a white, round tablet, with the letter 'T' on one side and a scoreline on the other side.

Your tablets are available in blister packs of 14 and 28 (not all pack sizes may be marketed).

Marketing Authorisation Holder

Clarendon Pharma Limited
19 King Street, Seagrave, Leicestershire, LE12 7LY, U.K.

Manufacturer:

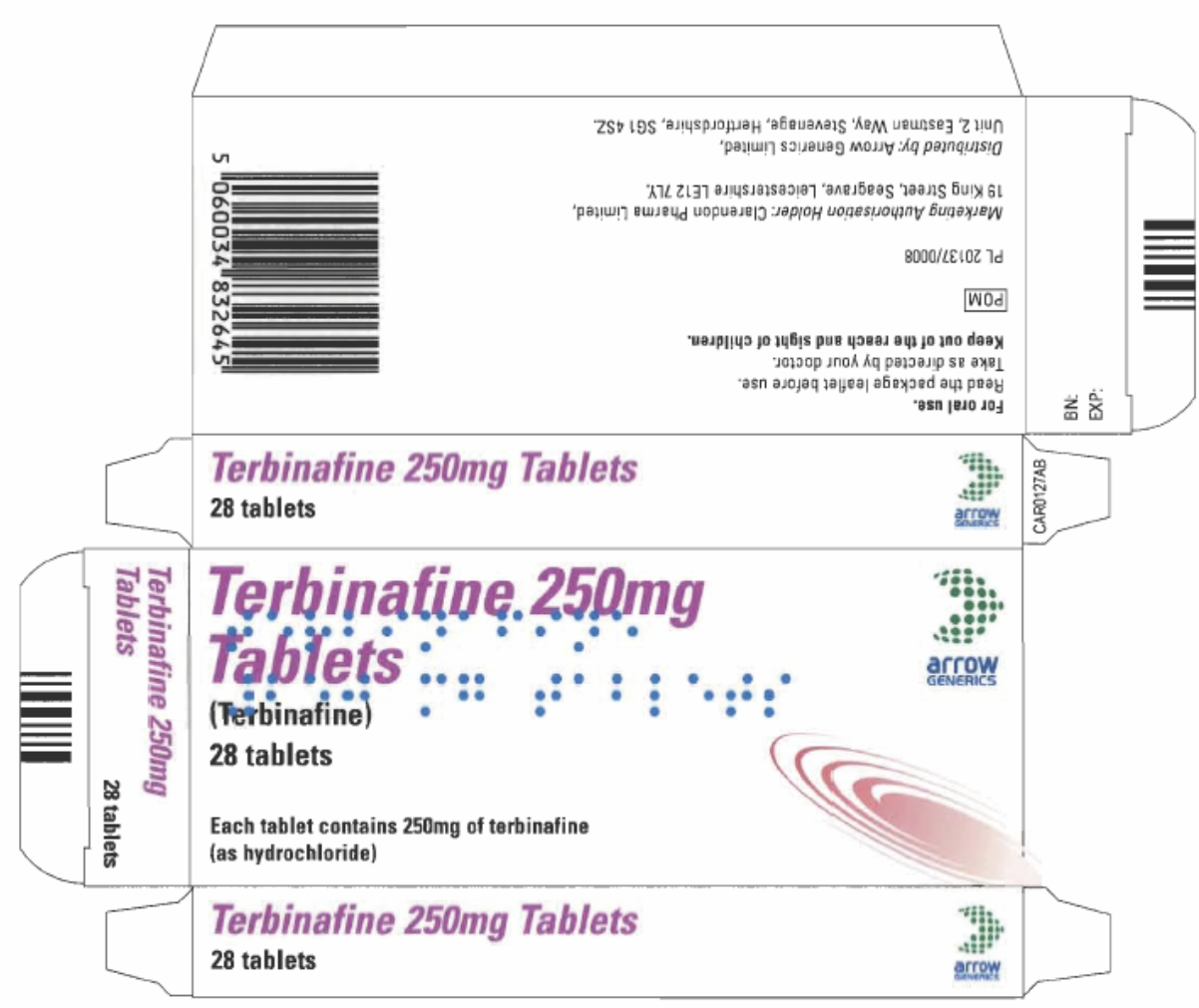
Arrow Pharm (Malta) Limited
Unit 62, Hal Far Industrial Estate, Hal Far, Malta.

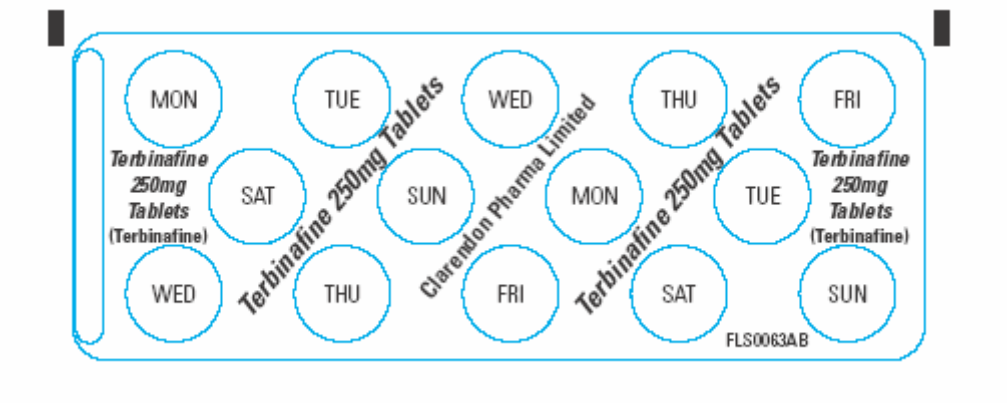
This leaflet was last approved in (MM/YYYY)

LFT0023AB

Module 4

Labelling





Module 5

Scientific discussion during initial procedure

1. INTRODUCTION

Background

These applications were submitted by Clarendon Pharma Limited for generic versions of Terbinafine, via the Decentralised (Mutual Recognition) Procedure. The originator product is Lamisil 250 mg Tablets authorised to Novartis Healthcare A/S in Denmark in May 1991.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Terbinafine 250mg Tablets in the treatment of the following indications could be approved:

Fungal infections of the skin and nails caused by dermatophytes such as Trichophyton (*T. rubrum, T. mentagrophytes, T. verrucosum, T. tonsurans, T. violaceum*), Microsporum canis and Epidermophyton floccosum such as tinea corporis, tinea cruris and tinea pedis, when oral therapy is considered appropriate due to the site, severity or extent of the infection.
Treatment of onychomycosis.

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

Marketing Authorisations were granted in Belgium, Denmark, Germany, Finland, Italy, Malta, The Netherlands, Norway, Portugal, Slovenia, Slovakia, Poland, Hungry and Czech Republic. The product names in these CMS's are:

Belgium	Terbinafine Arrow 250 mg Comprimes
Czech Republic	Terbinafini Arrow
Finland	Terbinafin Recept 250 mg Tabletti
Germany	Terbina-Q 250 mg Tabletten
Hungary	Terbinafine 250mg Tabletta
Italy	Terbinafina Arrow 250 mg Compresse
Malta	Terbinafine 250 mg Tablets
Netherlands	Terbinafine 250 mg Tabletten
Norway	Terbinafin Recept
Poland	Terbinafina 250mg Tabletki
Portugal	Terbinafina Arrowblue 250 mg Comprimidos
Slovakia	Terbinafin Arrow 250mg
Slovenia	Terbinafin Arrow 250mg tablete

Overall Benefit/Risk Assessment

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

2. QUALITY ASPECTS

I. INTRODUCTION

This is an abridged application for Terbinafine 250mg Tablets, submitted by Clarendon Pharma Ltd., under Article 10.1 [formerly 10.1a (iii)] of Directive 2001/83/EC, claiming 'essential similarity' to the brand leader product, Lamisil 250mg Tablets, PL 00101/0304, marketed by Novartis Pharmaceuticals (granted in the UK on 3rd October 1990).

Terbinafine is indicated for the treatment of fungal infections of the skin and nails and for ringworm where oral therapy is considered appropriate.

II. ACTIVE SUBSTANCE

The active substance is the subject of a DMF. This DMF has not been assessed previously in relation to Marketing Authorisations for products for the UK market.

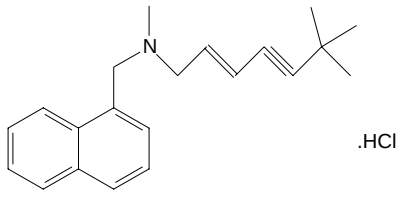
A copy of the letter of access to the DMF has been provided.

III. General Information

III.1.1 Nomenclature

rINN: Terbinafine hydrochloride
Chemical names:
(E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthylmethylamine hydrochloride
(E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalene methamine hydrochloride
Trans-N-methyl-N-(1-naphthylmethyl)-6,6-dimethylhept-2-en-4-ynyl-1-amine hydrochloride
CAS number: 78628-80-5

III.1.2 Structure



Molecular formula: $C_{21}H_{25}N.HCl$
MWt: 327.94

III.1.3 General properties

An odourless, white crystalline powder. Slightly soluble in acetonitrile; soluble in methanol.

Melting point: 195-198°C.

III.4 Control of Active substance

III.4.1 Specification

The active substance specification has been provided and is acceptable.

The finished product manufacturer's specification is consistent with that of the Active Substance Manufacturer (ASM). The finished product manufacturer (FPM) uses identical methods to the ASM where non-pharmacopoeial methodology is employed.
Following successful qualification of the ASM, reduced testing may be applied by the finished product manufacturer (description, identification, related substances, and assay). Full testing of selected batches would be carried out on a non-routine basis.

III.4.2 Analytical Procedures

Analytical procedures employed by the ASM have been provided and are acceptable.

III.4.3 Validation of Analytical Procedures

The validation of the ASM's analytical procedures has been described and is considered acceptable..

A satisfactory validation report is provided for the analytical method for determination of related substances employed by the finished product manufacturer.

III.4.4 Batch Analyses

Batch analyses of 2 production scale batches have been provided, with certificates of analysis from the ASM. The results are consistently well within the proposed specification.

Analytical results for another three batches of more or less commercial scale are provided in module 3.2S, with certificates of analysis from both the ASM and the finished product manufacturer.

The results are consistently well within the proposed specification.

III.7 Stability

III.7.3. Stability Data

Stability studies are appropriately designed and results provided support the retest interval proposed.

IV. MEDICINAL PRODUCT

IV.1 Description and Composition of the Medicinal product

The product is presented as white, round tablets, one side scored, with 'T' embossed on the opposite face. Qualitative tablet composition is given in Table 1, below:-

Table 1: Qualitative composition of Terbinafine 250mg Tablets

Ingredient	Function	Reference to standard
Terbinafine hydrochloride	Active substance	In house
Microcrystalline cellulose	Filler	Ph Eur
Colloidal anhydrous silica	Filler [*sic*]	Ph Eur
Hydroxypropylmethylcellulose	Binder/disintegrant	Ph Eur
Sodium starch glycollate	Disintegrant	Ph Eur
Magnesium stearate	Lubricant	Ph Eur
Purified water	Granulating solvent	Ph Eur

Container:
The tablets are packaged in PVC/PVdC/Al foil blisters.

Clinical trial formulae:
It is confirmed that the formulation of the batch of product used in the bioequivalence study was identical in composition to that given above.

IV.2 Pharmaceutical Development

The aim of the pharmaceutical development programme was the formulation of tablets that were easily manufactured, were stable in blister packs for three years and were essentially similar to the innovator product, Lamisil tablets, from the European market.

IV.2.1 Components of the Medicinal product

IV.2.1.1 Active substance

Active substance from the proposed source was used throughout the development programme.

Particle size analysis was performed by the finished product manufacturer. The results of the analysis of three batches of active substance used subsequently in the manufacture of the qualification batches (including the biobatch) have been provided, upon which the approved particle size specification was based.

IV.2.1.2 Excipients

Discussion of the role of each excipient in the formulation is provided. Since these are identical to those present in the brand leader, no further investigations have been reported. This may be accepted.

IV.2.2 Medicinal product

IV.2.2.1 Formulation development

All development work was carried out at one of the proposed finished product manufacturers. The quantitative formulation of the innovator product from the Italian market was obtained from the public domain (Italian Drug Index). An identical composition was developed for the applicant's product.

No further development work was reported. This can be accepted.

IV.2.2.2 Overages

There are none.

IV.2.2.3 Physicochemical and biological properties

Physicochemical analysis of the brand leader product, taken from the UK and Spanish markets, was performed.

The development of the dissolution method is discussed. Terbinafine hydrochloride active substance solubility was examined in a range of media and at different pH, as was the dissolution behaviour of a development batch of the applicant's product.

Comparative dissolution profiles of the applicant's product (the biobatch) and the brand leader product from a number of European markets, as well as Turkey, were obtained using the proposed test conditions.

In general, similar profiles were seen for all batches tested. The discriminatory capability of the method has not been specifically addressed; however, these conditions have been approved previously in relation to the testing of terbinafine tablet products.

Comparative impurity profiles for the applicant's product and the brand leader from the UK and Spain were determined. Very low levels of impurities were detected for all of the batches, with no detected impurities for the applicant's product.

IV.2.3 Manufacturing Process Development

The finished product manufacturer deduced that the formulation of the brand leader product suggested that a wet granulation manufacturing process was employed, and adopted the same approach.

Pre-formulation studies are stated to have been performed to determine the optimum processing parameters, such as amount of granulating fluid, mixer type and critical in-process controls – the results for which have not been reported. A laboratory scale batch was manufactured according to the proposed method, and found to exhibit favourable characteristics, thus the manufacturing process was concluded to be suitable.

IV.2.4 Container Closure System

Preliminary stability studies were performed under accelerated conditions for one batch of the UK reference product and 2 batches of the applicant's product (laboratory and pilot scale), looking at the stability of the product in the proposed packaging (opaque blisters), in transparent blisters and in an open dish. Samples were tested after storage for 2 weeks (open dish), or periodically up to six months (blisters). No degradation was apparent in the batches stored for 2 weeks in an open dish. Increases in water content and degradation products and a reduction in the percentage dissolved after 20 minutes were noted after six

months storage in the blisters, but these remained within the proposed specifications. The suitability of the proposed packaging was therefore considered to have been demonstrated, given that no reaction between packaging and product was noted and furthermore, that this is a standard packaging type for such products. This may be accepted.

IV.2.5 Microbiological Attributes

Microbial contamination is not considered to be an issue for a product of this type.

IV.2.6 Compatibility

Not applicable.

Given the similarity between the applicant's product and the brand leader, the development pharmaceutics investigations that have been reported are considered to be adequate.

IV.3 Manufacture

IV.3.1 Manufacturer

The finished product manufacturers have been named and are acceptable.

IV.3.2 Batch Formula

The proposed maximum batch size has been stated and the batch formulae provided,

IV.3.3 Description of Manufacturing Process and Process Controls

A flow-chart of the manufacturing process, detailing the in-process controls performed is provided.

A standard wet granulation method is employed.

IV.3.4 Control of Critical Steps and Intermediates

There are no designated intermediate products. The in-process controls are adequate for this type of manufacturing process. The sampling frequency during tabletting is given and the specifications applied have been provided.These are satisfactory.

IV.3.5 Process Validation and/or Evaluation

Satisfactory validation of the process has been performed on three batches manufactured at each manufacturing site. Different batches of active substance were used..

A detailed account of the validation investigations is provided. Critical steps were evaluated and suitable in-process controls performed.

All results were found to be within the proposed quality specifications, and provide satisfactory evidence of the robustness of the manufacturing process and its capability of consistently producing tablets of the required quality.

IV.4 Control of Excipients

IV.4.1 Specifications

All of the excipients used are covered by Ph Eur monographs and are stated to be tested in accordance with the same. The specifications and sample certificates of analysis are provided.

IV.4.2 Analytical Procedures

Ph Eur methodology is routinely applied.

IV.4.3 Validation of Analytical Procedure

None required.

IV.4.4 Justification of Specification

Since the excipients are controlled according to Ph Eur specifications, no further justification is necessary.

IV.4.5 Excipients of Human or Animal Origin

It is stated that there are no excipients of human or animal origin used in the manufacture. Suppliers' declarations are provided. Magnesium stearate is confirmed as being exclusively of vegetable origin.

IV.4.6 Novel Excipients

There are none.

IV.5 Control of Medicinal product

IV.5.1 Specification

The specification applied to the product at release and for the duration of its shelf-life has been provided. The frequency of testing is indicated, which is satisfactory.

IV.5.2 Analytical Procedures

Details of the analytical methods employed are provided. Most tests are performed using standard Ph Eur methodology. In-house HPLC methods are described for the identification and assay, determination of related substances and analysis of dissolution samples.

IV.5.3 Validation of Analytical Procedures

Validation summaries have been provided for the HPLC methods. These methods have been validated satisfactorily. Other methods are performed using pharmacopoeial methodology, for which no further validation data are required.

The method for dissolution sample analysis has been validated satisfactorily.

IV.5.4 Batch Analyses

Batch analytical data are presented for five production scale batches of the product from both finished product manufacturers. The results provide evidence that the product consistently meets the proposed specification.

IV.5.5 Characterisation of Impurities

No further characterisation of impurities, to that provided for the active substance, has been carried out. This is acceptable.

IV.5.6 Justification of Specification

Justification of the specification and limits is provided. The discussion provided is accepted.

IV.6 Reference Standards or Materials

Satisfactory CoAs are provided for the impurity and active substance standards. All of these were obtained from the ASM and are acceptable.

IV.7 Container Closure System

The tablets are packaged in PVC/PVdC/Al blisters. Certificates of analysis, details of the specifications and routine tests applied to the packaging components are provided, along with suppliers and technical data. These are satisfactory.

Confirmation that the plastic materials conform to the relevant EU food contact legislation is provided.

IV.8 Stability

IV.8.1 Stability Summary and Conclusion

Stability studies under long-term and accelerated conditions in line with ICH recommendations have been initiated on one pilot batch and three commercial scale batches of product, packaged as proposed for marketing from the first site of manufacture. Samples were tested according to the proposed shelf-life specification, using the methods described above. Long-term stability data has been presented for all batches at the 36 month time point.

For all four batches accelerated data is presented. No out of specification results were reported.

Three months stability data have been provided for three commercial scale batches manufactured at the alternative site under long-term conditions. No out of specification results were reported.

The stability data presented are satisfactory. A shelf life of 3 years is supported with no special storage conditions.

IV.8.2 Post-approval Stability Protocol and Stability Commitment

It is stated that the stability studies will continue for the proposed duration (three years long-term storage), and any out of specification results will be reported. This is acceptable.

IV.8.3 Stability Data

The data confirm that there are no significant changes in the product over the time period for which results are available, with all of the batches remaining within specification under both storage conditions. Individual known and unknown impurities were consistently well below the specification limit.

V. APPENDICES

V.1 Facilities and Equipment

Not applicable.

V.2 Adventitious Agents Safety Evaluation

Not applicable.

V.3 Novel Excipients

Not applicable.

VI. REGIONAL INFORMATION

TSE declarations are provided for all of the excipient suppliers. Additionally, a declaration is provided from the active substance manufacturer, confirming that no materials of animal origin are used in the manufacture of the active substance.

VII.ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

SPC

This is satisfactory, from a pharmaceutical point of view.

PIL

This is satisfactory, from a pharmaceutical point of view.

Labelling

This is satisfactory, from a pharmaceutical point of view.

VII.1 Other information

VII.1.2 Bioanalytical methods

Blood samples from the subjects in the biostudy were processed to determine terbinafine content.

This analytical method has been validated appropriately.

VII.1.3 Bioavailability, bioequivalence

The bioequivalence study was carried out between September and November 2002.

The study design was an open-label, single dose two period cross-over undertaken with 28 healthy volunteers (25 completed) in the fasting state, comparing the applicant's product with the corresponding strength of the reference product, Lamisil 250, taken from the UK market. There was a washout period of 14-16 days between treatments.

Blood samples were taken prior to dosing and then intermittently post administration. Primary pharmacokinetic variables that were determined were $AUC_{0-\infty}$ and C_{max}, while T_{max}, $t_{½.z}$, $AUC_{0-tlast}$ and mean residence time (MRT) were also calculated. Results are displayed in table 6a, below, with analysis of the primary variables in table 6b. Geometric mean values are displayed here, results are also presented in terms of arithmetic means in the study report.

Table 6a: Pharmacokinetic parameters from Terbinafine Biostudy, 244/2002

Variable	**Reference (Lamisil)**			**Test**		
	Mean	**SD**	**Range**	**Mean**	**SD**	**Range**
C_{max} (ng/ml)	1093	1.42	720-2689	965	1.49	446-2081
T_{max} (h)	1.50	-	0.50-3.00	1.50	-	0.50-3.00
$AUC_{0-tlast}$ (ng.h/ml)	4246	1.36	2681-9733	4128	1.45	2319-11492
$AUC_{0-\infty}$ (ng.h/ml)	4663	1.37	2918-11972	4630	1.47	2548-13764
$C_{max}/AUC_{0-\infty}$ (1/h)	0.23	1.25	0.16-0.36	0.21	1.31	0.11-0.32
$t_{½.z}$ (h)	47.2	1.31	30.5-83.8	53.4	1.34	24.7-82.5
MRT (h)	29.6	1.40	17.1-64.5	34.9	1.49	14.6-74.4

Table 6b: Statistical analysis of primary pharmacokinetic parameters

Variable	**Mean ration (point estimate)**	**90% Confidence Interval**
C_{max} (ng/ml)	88.0	80.8-95.9
$AUC_{0-\infty}$ (ng.h/ml)	98.9	93.5-103

It can be seen that the 90% confidence intervals for C_{max} and $AUC_{0-\infty}$ fall within the range of 80-125%, which is required for bioequivalence to be concluded. The study has, therefore, demonstrated that the test and reference product behave comparably in terms of the rate and extent of their absorption.

VII.1.4 Essential similarity

The applicant's product is accepted as being pharmaceutically equivalent to the reference product, being qualitatively and quantitatively identical to an innovator product formulation on the European market. Comparable *in vitro* dissolution behaviour has been demonstrated.

The products have also been satisfactorily demonstrated as bioequivalent and, thus, the applicant's claim of 'essential similarity' is supported.

VII.2.1 Administrative

VII.2.2 Comment on Quality Overall Summary

The Quality Overall Summary has been prepared by a pharmacist. His CV has been provided, and indicates that he is appropriately qualified to perform this role.

It is an adequate, non-critical summary of the data provided in Module 3.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

This data package is generally of an acceptable quality. There are no major objections to the grant of a Marketing Authorisation.

3. NON-CLINICAL ASPECTS

These applications for a generic product claim essential similarity to Lamisil Tablets (Novartis Pharmaceuticals UK Limited), which has been licensed within the EEA for over 10 years.

No new non-clinical data has been supplied with these applications, however a Non-Clinical overview, summarising relevant non-clinical studies has been provided. This is satisfactory.

For further non-clinical information relevant to this product, the reader is referred to the non-clinical data presented in Module 4.

4. CLINICAL ASPECTS

1. INTRODUCTION

Terbinafine is a broad spectrum anti-fungal agent which acts by inhibiting fungal sterol synthesis.

2. REGULATORY STATUS

This is an abridged application for terbinafine tablets, 250 mg. The application is submitted under Article 10.1 [formerly article 10.1(a)(iii)] of Directive 2001/83/EC. The applicant claims essential similarity to Lamisil tablets 250 mg licensed to Novartis (UK) on 3rd October 1990 (PL 00101/0304).

3. INDICATIONS

From the SPC

1. 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.
2. 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.
3. Treatment of onychomycosis.

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

3.2 Posology and method of administration

The SPC recommends the usual dose is 250 mg once daily, duration depending on indication. Children: not recommended
Patients with impaired renal function or liver function, dose referenced in Section 4.4.

4. CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics - General

Terbinafine is well absorbed orally with a C_{max} of approximately 1 mg/L at two hours after a single 250 mg oral tablet. Bioavailability is 70% and food delays absorption by about an hour, but does not affect bioavailability. Kinetics are linear between 125-750 mg doses and steady state plasma is reached after 10-14 days in healthy volunteers with 125 or 250 mg daily doses.
Terbinafine is lipophilic with a large volume of distribution of about 1,000-2,000 L. It is >95% plasma protein bound and tissue concentrations are higher in skin and nails, than in plasma.
It has extensively metabolised in the liver, partly first pass, and oxidised by CYP enzymes. At least 7 CYP enzymes, particularly CYP2C9, CYP1A2, CYP3A4, and CYP2C8, are involved and it is a competitive inhibitor of CYP2D6. There are nearly 15

known inactive metabolites. Although it inhibits CYP2D6, its metabolism by multiple enzyme pathways means few interactions, other than anti-mycotics and important interactions with tricyclic antidepressants.

4.2 Pharmacokinetics - Bioequivalence Study

This was an open label, laboratory blind, single dose, randomised, two period cross over trial in healthy volunteers. There were 28 volunteers recruited. Of these, two dropped out and one discontinued, so that 25 completed.
The study was carried out between September and November 2002. The test product was terbinafine 250 mg tablets and the reference product Lamisil 250 mg tablets from Sandoz, UK.
The applicant claims the study was carried out to good clinical practice.

Results

Table 1 – Terbinafine mean pharmacokinetic data

Variable	Lamisil (reference)	Terbinafine (test)
C_{max} (ng/ml)	1093	965
T_{max} (h)	1.50	1.50
AUC_{α} (0-∞) (ng.h/ml)	4663	4630
T½ (h)	47	53

The Test versus Reference ratios were 99% (94-105 90%CI) for AUC and 88% (81-96) for C_{max}.

4.3 Pharmacodynamics

Terbinafine blocks ergosterol biosynthesis in the fungal cell wall, inhibiting enzyme squalene epoxidase, leading to toxic accumulation of squalene. Terbinafine has a low affinity to mammalian cells compared to fungal cells although the ergosterol synthesis is similar to cholesterol synthesis. The mean MIC and the mean minimal fungicidal concentration (MFC) for terbinafine in 39 dermatophyte isolates is 0.004 μg/ml, a value lower than other antifungal agents. In contrast to ketoconazole, terbinafine has little effect on mammalian steroid hormone synthesis.

4.4 Clinical Pharmacology - Clinical Assessor's Comments

The applicant appears to have shown bioequivalence for terbinafine within accepted limits.

5. EFFICACY

Efficacy is reviewed in the Clinical Overall Summary report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

6. SAFETY

Safety is reviewed in the Clinical Overall Summary report. The reference product is established and the main basis of the application depends upon the bioequivalence study. The present product has not been marketed and no post marketing surveillance data are available.

7. CLINICAL OVERALL SUMMARY

This was written by a suitably qualified person.

8. SUMMARY OF PRODUCT CHARACTERISITCS

Clinically satisfactory.

9. PATIENT INFORMATION LEAFLET

Clinically satisfactory.

10. CONCLUSIONS

The applicant appears to have shown bioequivalence to the UK market leader.
The clinical data appears satisfactory.

5. OVERALL CONCLUSION

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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Terbinafine 250mg Tablets and Lamisil 250mg Tablets.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

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 product and the innovator product 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.

Module 6

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome