Public Assessment Report

Decentralised Procedure

Terbinafine 125 mg tablets
Terbinafine 250 mg tablets

Terbinafine Hydrochloride

UK/H/1138/001/DC
UK/H/1138/002/DC

Aurobindo Pharma Limited
Lay summary

The Medicines Healthcare products Regulatory Agency granted Aurobindo Pharma Limited Marketing Authorisations (licences) for the medicinal products Terbinafine 125 mg tablets and Terbinafine 250 mg tablets. These medicines are available on prescription only.

Terbinafine 125 mg and 250 mg tablets contain the active ingredient terbinafine. Terbinafine belongs to a group of medicines called antifungals. It is used for the treatment of fungal infections of the skin (including those between the fingers and toes) and of the nails.

The test product was considered to be a generic version of the reference product, Lamisil 250 mg tablets (Sandoz Pharmaceuticals), based on the bioequivalence study submitted. No new safety issues arose as a result of this study.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Terbinafine 250 mg tablets and Terbinafine 125 mg tablets outweigh the risks; hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about decentralised procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflet</td>
<td>19</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>22</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>28</td>
</tr>
</tbody>
</table>

- 1 Introduction
- 2 Quality aspects
- 3 Non-clinical aspects
- 4 Clinical aspects
- 5 Overall conclusions
### Module 1

#### Information about decentralised procedure

| **Name of the product in the reference member state** | Terbinafine 125 mg tablets  
Terbinafine 250 mg tablets |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of the active substance (INN)</strong></td>
<td>Terbinafine hydrochloride</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Anti-fungal agent, D01BA02</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength</strong></td>
<td>Tablet, 125 mg &amp; 250 mg</td>
</tr>
</tbody>
</table>
| **Reference numbers for the decentralised procedure**| UK/H/1138/001/DC  
UK/H/1138/002/DC |
| **Reference member state**                           | UK                          |
| **Member states concerned**                          | Austria, Belgium, Czech Republic, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, The Netherlands, Poland and Portugal |
| **Date of start of the procedure**                   | 18 July 2007                |
| **End date of decentralised procedure**              | 04 September 2008           |
| **Marketing authorisation number**                   | PL 20532/0136  
PL 20532/0113 |
| **Name and address of the authorisation holder**     | Aurobindo Pharma Limited  
Ares, Odyssey Business Park  
West End Road  
South Ruislip HA4 6QD  
United Kingdom |
Module 2

Summary of Product Characteristics

PL 20532/0136:

1 NAME OF THE MEDICINAL PRODUCT
Terbinafine 125 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 125 mg terbinafine (as 140.625 mg terbinafine hydrochloride).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White to off-white, round uncoated, biconvex bevelled edge tablets having ‘D’ debossed on one side and ‘56’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of fungal infections of the skin caused by terbinafine sensitive dermatophytes in cases of 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 caused by terbinafine sensitive dermatophytes.

Consideration should be given to official guidance concerning the appropriate use and prescription of antifungals.

4.2 Posology and method of administration

Adults:
250 mg once daily however, the duration of treatment will vary according to the indication and the severity of the infection.

Skin Infections:
Duration of the treatment
The likely durations of treatments are as follows:

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

Onychomycosis
The duration of treatment is usually between 6 weeks and 3 months. Treatment of 6 weeks for onychomycosis of the finger nails is generally sufficient. Regarding
onychomycosis of the toe nails, a 12 week treatment is usually sufficient, although a few patients with poor nail growth may require a longer treatment duration (6 months or longer). Complete resolution of the signs and symptoms of infection may not occur until several months after cessation of the treatment. This corresponds to the time needed for a healthy nail growth.

**Elderly:**
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 50 ml/minute or serum creatinine of more than 300 µmol/l) should receive half the normal dose.

**Hepatic insufficiency:**
Terbinafine is not recommended for patients with chronic or active liver disease. In case of benefit-risk assessment the benefit outweighs the risks, a lower dosage should be initiated in case of hepatic insufficiency. In patients with pre-existing mild or serious liver disease clearance of terbinafine may be reduced (see section 5.2). See also section 4.4 with regard to patients with liver impairment.

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

### 4.3 Contraindications
- Hypersensitivity to terbinafine or to any of the excipients.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment.

### 4.4 Special warnings and precautions for use
The therapeutic use of terbinafine in patients with chronic or active liver disease has not been studied and is not recommended (see also section 4.2). Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that clearance of terbinafine may be reduced by about 50%. Where benefit outweighs the risks, a lower dosage should be initiated in case of hepatic insufficiency.

Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within 2 months of starting treatment. Very rarely terbinafine can cause liver failure in patients with or without preexisting 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 presents with signs or symptoms suggestive of liver dysfunction such as pruritus, persistent nausea, anorexia or tiredness, jaundice, vomiting, fatigue, abdominal pain or dark urine or pale stools, hepatic origin should be verified and treatment should be immediately stopped.

Terbinafine should be used with caution in patients with psoriasis, as very rare cases of exacerbation of psoriasis have been reported.
Terbinafine should be used with caution in patients with impaired renal function. Patients with reduced renal function (creatinine clearance $\geq 30 < 50$ ml/min or serum creatinine $> 300 \mu$mol/l) should receive half the normal dose.

Agranulocytosis and toxic epidermal necrolysis may very rarely occur in patients treated with oral terbinafine. Hence, patients should discontinue immediately the treatment and see a physician if the following symptoms occur: high fever, sore throat or other infections, pruritus, disseminated cutaneous disorders or cutaneous disorders with involvement of the mucosa (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction
The plasma clearance of terbinafine may be accelerated by drugs, which induce metabolism (such as rifampicin) and may be inhibited by drugs, which inhibit cytochrome P450 (such as cimetidine). When 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), $\beta$-blockers, selective serotonin reuptake inhibitors (SSRIs), the antiarrhythmic agents (e.g. flecainide, propafenone) and monoamine oxidase inhibitors (MAO-Is) type B. These patients should be carefully monitored. In vitro terbinafine has been shown to be metabolised by at least 7 CYP-iso-enzymes, mainly by the iso-enzymes CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19.

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 an irregular cycle) have been reported in patients taking terbinafine concomitantly with oral contraceptives.

4.6 Pregnancy and lactation

Pregnancy:
Fetal toxicity and fertility studies in animals suggest no adverse effects. There are no adequate data from the use of terbinafine in pregnant women, Therefore Terbinafine should not be given during pregnancy.

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

4.7 Effects on ability to drive and use machines
Terbinafine has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects
Adverse reactions are listed by frequency:

- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
Very rare (<1/10,000),
not known (cannot be estimated from the available data)

The following undesirable effects have been observed:

**Investigations:**
*Common:* Increased hepatic enzymes level (see section 4.4).

**Blood and the lymphatic system disorders:**
*Very rare:* Agranulocytosis, neutropenia, thrombocytopenia.

**Nervous system disorders:**
*Common:* Headache.
*Rare:* Dizziness, hypoesthesia, paresthesia.
*Very rare:* Vertigo

**Gastrointestinal disorders:**
*Common:* Fullness, mild abdominal pain, diarrhoea, dyspepsia, nausea.
*Uncommon:* Ageusia or dysgeusia (age over 65 years and low body mass index are risk factors), usually reversible within a few weeks or months after cessation of the treatment.

Very rare cases of prolonged taste disturbance have been reported, sometimes leading to a decrease of food intake and significant weight loss.

**Skin and subcutaneous tissue disorders:**
*Very common:* Rash, urticaria.
*Very rare:* Serious skin reactions (e.g. Stevens-Johnson’s syndrome, toxic epidermal necrolysis, photosensitivity and angioneurotic oedema) have been reported.

If a progressive skin rash develops treatment should be discontinued.
Psoriasisiform eruptions or exacerbation psoriasis.
Hair loss, although a causal relationship has not been established.

**Musculoskeletal, connective tissue and bone disorders:**
*Very Common:* Arthralgia and myalgia.

These may occur as part of a hypersensitivity reaction in association with allergic skin reactions.

**Metabolism and Nutritional disorders:**
*Common:* Anorexia (Loss of appetite).

**General disorders and administration site conditions:**
*Rare:* Fatigue, malaise.

**Immune system disorders:**
*Rare:* Incidence of allergic reactions (including anaphylaxis).
*Very rare:* Manifestation or aggravation of cutaneous or systemic lupus erythematosus.

**Hepato-biliary disorders:**
Rare: Hepatobiliary dysfunction especially cholestasis, and in rare cases liver failure, which in some instances has lead to hepatic transplantation or to death (see section 4.4).

**Reproductive system and breast disorders:**
Very rare: Menstrual disturbance, breakthrough bleeding.

**Psychiatric disorders:**
Very rare: Anxiety, depression.

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

**Mechanism of action:**
Terbinafine interferes specifically with fungal sterol biosynthesis at an early stage. 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 250 mg 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 by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19.

Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. The elimination half-life is 17 hours. There is no evidence of accumulation in the plasma.

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

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 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumours was observed in males at the highest dosage level of 69 mg/kg a day. The changes, which may be associated with peroxisome proliferation, have been shown to be species-specific since they were not seen in 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
Cellulose microcrystalline
Sodium starch glycolate (type A)
Silica colloidal anhydrous
Hypermellose
Magnesium stearate

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years.

6.4 **Special precautions for storage**
Store in the original package in order to protect from light.

6.5 **Nature and contents of container**
PVC/PVDC/Aluminum blister pack
Pack sizes: 7, 8, 12, 14, 28, 42 and 56 tablets.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20532/0136

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/06/2009

10 **DATE OF REVISION OF THE TEXT**
18/06/2009
1 NAME OF THE MEDICINAL PRODUCT
Terbinafine 250 mg tablets

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

3 PHARMACEUTICAL FORM
Tablet
White to off-white, round, uncoated, biconvex bevelled edge tablets with breakline
and ‘D’ debossed on one side and ‘74’ on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of fungal infections of the skin caused by terbinafine sensitive
dermatophytes in cases of 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 caused by terbinafine sensitive dermatophytes.

Consideration should be given to official guidance concerning the appropriate use and
prescription of antifungals.

4.2 Posology and method of administration
Adults:
250 mg once daily however, the duration of treatment will vary according to the
indication and the severity of the infection.

Skin Infections:
Duration of the treatment
The likely durations of treatments are as follows:

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

Onychomycosis
The duration of treatment is usually between 6 weeks and 3 months. Treatment of 6
weeks for onychomycosis of the finger nails is generally sufficient. Regarding
onychomycosis of the toe nails, a 12 week treatment is usually sufficient, although a
few patients with poor nail outgrow may require a longer treatment duration (6 months
or longer). Complete resolution of the signs and symptoms of infection may not occur
until several months after cessation of the treatment. This corresponds to the time
needed for a healthy nail growth.
**Elderly:**
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 50 ml/minute or serum creatinine of more than 300 µmol/l) should receive half the normal dose.

**Hepatic insufficiency:**
Terbinafine is not recommended for patients with chronic or active liver disease. In case of benefit-risk assessment the benefit outweighs the risks, a lower dosage should be initiated in case of hepatic insufficiency. In patients with pre-existing mild or serious liver disease clearance of terbinafine may be reduced (see section 5.2). See also section 4.4 with regard to patients with liver impairment.

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

4.3 Contraindications
- Hypersensitivity to terbinafine or to any of the excipients.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment.

4.4 Special warnings and precautions for use
The therapeutic use of terbinafine in patients with chronic or active liver disease has not been studied and is not recommended (see also section 4.2). Single dose pharmacokinetic studies in patients with pre-existing liver disease have shown that clearance of terbinafine may be reduced by about 50%. Where benefit outweighs the risks, a lower dosage should be initiated in case of hepatic insufficiency.

Rarely, cases of cholestasis and hepatitis have been reported, these usually occur within 2 months of starting treatment. Very rarely terbinafine can cause liver failure in patients with or without preexisting 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 presents with signs or symptoms suggestive of liver dysfunction such as pruritus, persistent nausea, anorexia or tiredness, jaundice, vomiting, fatigue, abdominal pain or dark urine or pale stools, hepatic origin should be verified and treatment should be immediately stopped.

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

Terbinafine should be used with caution in patients with impaired renal function. Patients with reduced renal function (creatinine clearance ≥30 < 50 ml/min or serum creatinine > 300 µmol/l) should receive half the normal dose.
Agranulocytosis and toxic epidermal necrolysis may very rarely occur in patients treated with oral terbinafine. Hence, patients should discontinue immediately the treatment and see a physician if the following symptoms occur: high fever, sore throat or other infections, pruritus, disseminated cutaneous disorders or cutaneous disorders with involvement of the mucosa (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

The plasma clearance of terbinafine may be accelerated by drugs, which induce metabolism (such as rifampicin) and may be inhibited by drugs, which inhibit cytochrome P450 (such as cimetidine). When 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 serotonin reuptake inhibitors (SSRIs), the antiarrhythmic agents (e.g. flecaïnide, propafenone) and monoamine oxidase inhibitors (MAO-Is) type B. These patients should be carefully monitored.

*In vitro* terbinafine has been shown to be metabolised by at least 7 CYP-iso-enzymes, mainly by the iso-enzymes CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19.

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 an irregular cycle) have been reported in patients taking terbinafine concomitantly with oral contraceptives.

4.6 Pregnancy and lactation

**Pregnancy:**
Fetal toxicity and fertility studies in animals suggest no adverse effects. There are no adequate data from the use of terbinafine in pregnant women, Therefore Terbinafine should not be given during pregnancy.

**Lactation:**
Terbinafine is excreted in breast milk and therefore nursing mothers should not receive Terbinafine whilst breast-feeding.

4.7 Effects on ability to drive and use machines
Terbinafine has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects
Adverse reactions are listed by frequency:

- **Common** (≥1/100 to <1/10)
- **Uncommon** (≥1/1,000 to <1/100)
- **Rare** (≥1/10,000 to <1/1,000)
- **Very rare** (<1/10,000),
  not known (cannot be estimated from the available data)

The following undesirable effects have been observed:
Investigations:
*Common:* Increased hepatic enzymes level (see section 4.4).

**Blood and the lymphatic system disorders:**
*Very rare:* Agranulocytosis, neutropenia, thrombocytopenia.

*Nervous system disorders:*
*Common:* Headache.
*Rare:* Dizziness, hypoaesthesia, paresthesia.
*Very rare:* Vertigo

**Gastrointestinal disorders:**
*Common:* Fullness, mild abdominal pain, diarrhoea, dyspepsia, nausea.
*Uncommon:* Ageusia or dysgeusia (age over 65 years and low body mass index are risk factors), usually reversible within a few weeks or months after cessation of the treatment.
Very rare cases of prolonged taste disturbance have been reported, sometimes leading to a decrease of food intake and significant weight loss.

**Skin and subcutaneous tissue disorders:**
*Very common:* Rash, urticaria.
*Very rare:* Serious skin reactions (e.g. Stevens-Johnson’s syndrome, toxic epidermal necrolysis, photosensitivity and angioneurotic oedema) have been reported.
If a progressive skin rash develops treatment should be discontinued.
Psoriasiform eruptions or exacerbation psoriasis.
Hair loss, although a causal relationship has not been established.

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

**Metabolism and Nutritional disorders:**
*Common:* Anorexia (Loss of appetite).

**General disorders and administration site conditions:**
*Rare:* Fatigue, malaise.

**Immune system disorders:**
*Rare:* Incidence of allergic reactions (including anaphylaxis).
*Very rare:* Manifestation or aggravation of cutaneous or systemic lupus erythematosus.

**Hepato-biliary disorders:**
*Rare:* Hepatobiliary dysfunction especially cholestasis, and in rare cases liver failure, which in some instances has lead to hepatic transplantation or to death (see section 4.4).

**Reproductive system and breast disorders:**
*Very rare:* Menstrual disturbance, breakthrough bleeding.
Psychiatric disorders:
Very rare: Anxiety, depression.

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

Mechanism of action:
Terbinafine interferes specifically with fungal sterol biosynthesis at an early stage.
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 250 mg 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 by
CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19.
Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine. The elimination half-life is 17 hours. There is no evidence of accumulation in the plasma.

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

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 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumours was observed in males at the highest dosage level of 69 mg/kg a day. The changes, which may be associated with peroxisome proliferation have been shown to be species-specific since they were not seen in 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
Cellulose microcrystalline
Sodium starch glycolate (type A)
Silica colloidal anhydrous
Hypromellose
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.
6.4 **Special precautions for storage**
Store in the original package in order to protect from light.

6.5 **Nature and contents of container**
PVC/PVDC/Aluminum blister pack
Pack sizes: 7, 8, 14, 28, 30, 42, 56 and 98 tablets.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20532/0113

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
18/06/2009

10 **DATE OF REVISION OF THE TEXT**
18/06/2009
Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

Terbinafine 125 mg tablets
Terbinafine 250 mg tablets

(Terbinafine)

Read all of this leaflet carefully before you start using 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 use Terbinafine
3. How to use Terbinafine
4. Possible side effects
5. How to store Terbinafine
6. Further information

1. WHAT TERBINAFINE IS AND WHAT IT IS USED FOR

Terbinafine belongs to a group of medicines called antifungals. It is used for the treatment of fungal infections of the skin (including those in between the fingers and toes) and of the nails.

2. BEFORE YOU USE TERBINAFINE

Do not use Terbinafine
- If you are allergic (hypersensitivity) to terbinafine or any of the other ingredients of Terbinafine.
- If you have a severe kidney problem.
- If you have a severe liver problem.

Take special care with Terbinafine
- If you have liver problems or a disease which may affect your liver.
- If you have psoriasis.
- If you have kidney problems.
If any of the above warnings applies to you or has applied to you in the past, consult your doctor.

Taking other medicines
Please tell to your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription:
- the antibiotic, rifampicin (decreases the level of terbinafine in your blood).
- cimicifugine (a medicine for stomach ulcers and heartburn), increases the level of terbinafine in your blood.
- medicines used to treat depression such as chlorpromazine, lọpetramine or paroxetine.
- certain medicines used to treat Parkinson’s disease such as monoamine oxidase inhibitors e.g. selegiline.
- medicines used to treat high blood pressure or heart problems such as atenolol or carvedilol (beta blockers).
- oral contraceptives (the pill). Irregular periods and abnormal menstrual bleeding which may be between periods may occur in female patients.
- flecainide and propafenone, which are used to treat heart flutters (arrhythmias).

Please note that the above medicines may be known to you by other names. Always thoroughly check the information leaflet of the medicines you are already using and check with your doctor or pharmacist before taking Terbinafine if you are taking any of the above sorts of medicines.

Pregnancy and breast-feeding
If you are pregnant, think you are pregnant or are breast-feeding; you should not take Terbinafine 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 or pharmacist for advice before taking any medicine.

Taking Terbinafine with food and drink
Taking food and drink has no influence on terbinafine treatment.

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

3. HOW TO USE TERBINAFINE

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

Dosage

Adults:
The dose you are prescribed will depend on the type of infection and how bad it is.
The usual dose is 250 mg Terbinafine 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 kidney problems, your doctor may prescribe half the recommended dose.

Duration of treatment:
Your doctor will tell you how long your treatment with terbinafine will last.
- For general fungal skin infections, your treatment will probably last for 4 weeks.
- Treatment for skin infections affecting the groin or body will normally last between 2 to 4 weeks and those involving feet may last between 2 to 6 weeks.
- For nail infections, your treatment may last between 8 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 take more Terbinafine than you should
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. You may feel dizzy, sick and have a headache and/or stomach pain.

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

If you stop taking Terbinafine
Do not stop taking terbinafine without consultation with your doctor, even if the infection heals.
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 can cause side effects, although not everybody gets them.

The following side effects have been observed:

You should stop taking your tablets and see your doctor immediately if:
- you experience symptoms of angioedema / anaphylaxis, such as:
  - swollen face, tongue or pharynx
  - difficulty in swallowing
  - hives
  - difficulties in breathing
  - feeling faint
  - you experience skin reactions such as weals, blisters, or a progressive rash
  - you have abnormalities of liver function. Symptoms 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.

Very common (more than 1 in 10 patients)
- Joint pain (arthralgia) and muscle pain (myalgia) can occur in association with allergic skin rashes.
- Rash, reddening of skin with itching and hives (urticaria). If progressive skin rash occurs, the treatment must be discontinued.

Common (in more than 1 in 100 patients, but less than 1 in 10 patients):
- Headache.
- Loss of appetite
- Stomachache, feeling of fullness, diarrhoea indigestion (dyspepsia), feeling sick (nausea).
- Increased hepatic enzyme levels

Uncommon (in more than 1 in 1,000 patients, but less than 1 in 100 patients):
- Loss or decrease of the sense of taste (ageusia or dysgeusia). This usually resolves slowly once you have stopped taking the medicine. Very rare cases of prolonged taste disturbances have been reported, sometimes leading to a decrease of food intake and significant weight loss.

Rare (in more than 1 in 10,000 patients, but less than 1 in 1,000 patients):
- Incidence of allergic reactions (including anaphylaxis).
- Pins and needles sensation (paraesthesias), numbness (hypoesthesia) and dizziness.
- Abnormal liver function, including liver inflammation (hepatitis) and jaundice (yellowing of the skin and eyes).
- Tiredness (fatigue), vague illness (malaise).

Very rare (in less than 1 in 10,000 patients, including isolated reports):
- Reductions in the number of different types of blood cells which may increase the risk of severe infection, bleeding or may cause shortness of breath and tiredness (agranulocytosis, neutropenia, thrombocytopenia).
- A Condition which may cause a very wide variety of symptoms such as joint pain, kidney problems, rash and fever (systemic lupus erythematosus).
- Anxiety and depression.
- Stevens-Johnson syndrome (a serious illness with blistering of the skin, mouth, eyes and genitals).
- Hair loss.
- Toxic epidermal necrolysis (a serious illness with blistering and loss of the skin).
- Menstrual disturbances such as abnormal menstrual bleeding which may be between periods, and an irregular cycle.
- Sensation of dizziness (vertigo).
- Serious allergic reactions, which causes swelling of the face or throat (angio oedema).
- Increased sensitivity of your skin to sunlight.
- Psoriasis or eruptions or exacerbation of psoriasis.

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.

Store in the original package in order to protect from light.

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

6. FURTHER INFORMATION

What Terbinafine contains
- The active substance is terbinfine.
  Each tablet contains 125 mg of terbinafine (as terbinafine hydrochloride).
  Each tablet contains 250 mg of terbinafine (as terbinafine hydrochloride).
- The other ingredients are cellulose microcrystalline, sodium starch glycolate (type A), silica colloidal anhydrous, hypromellose and magnesium stearate.

What Terbinafine looks like and contents of the pack
Tablets.
125 mg: White to off-white, round uncoated, biconvex bevelled edge tablets having ‘D’ debossed on one side and ‘50’ on the other side.
250 mg: White to off-white, round uncoated, biconvex bevelled edge tablets with beeline and ‘D’ debossed on one side and ‘74’ on the other side. The tablet can be divided into equal halves.

Terbinafine 125 mg tablets are available in PVC/PVDC/Aluminum blister packs of 7, 8, 12, 14, 28, 42 and 56 tablets.
Terbinafine 250 mg tablets are available in PVC/PVDC/Aluminum blister packs of 7, 8, 14, 28, 30, 42, 56 and 98 tablets.
Not all pack sizes may be marketed.

Marketing Authorization Holder
Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruisslip HA4 6QD
United Kingdom

Manufacturer
Mlipharma Limited,
Ares, Odyssey Business Park,
West End Road,
South Ruisslip HA4 6QD,
United Kingdom.
or
Pfizer Service Company BVBA
Hooge Weel 10
B-1500 Zaventem, Belgium
or
Pfizer PGM
Zone Industrielle
29. route des industries
37930 Pock-Sur-Cisse, France

This medicinal product is authorised in the Member States of the EEA under the following names:

- Austria: Terbinafin/Aurobindo 125 mg, 250 mg Tabletten
- Belgium: Terbinafine/Aurobindo 125 mg, 250 mg tablets
- Czech Republic: Terbinafine/Aurobindo 125 mg, 250 mg comprimés
- Finland: Terbinafine/Aurobindo 125 mg, 250 mg tablettar
- France: THERBIFINE/PFIZER 125 mg, 250 mg, comprimé
- Germany: Terbinafine/Aurobindo 125 mg, 250 mg Tabletten
- Greece: Terbinafine/Aurobindo 125 mg, 250 mg Soriax
- Hungary: Terbinafine/Aurobindo 125 mg, 250 mg tabletták
- Ireland: Terbinafine/Aurobindo 125 mg, 250 mg tablets
- Italy: Terbinafine/Aurobindo 125 mg, 250 mg compresse
- Poland: Terbinafine/Aurobindo
- Portugal: Terbinafine/Aurobindo
- Spain: THERBIFINE/AUROBINDO 125 mg, 250 mg comprimidos EFG
- The Netherlands: Terbinafine/Aurobindo 125 mg, 250 mg tabletten

This leaflet was last approved in 05/2009.
Module 4

Labelling

Foil:

Terbinafine 250 mg tablets
Terbinafine Aurobindo Pharma Limited
Terbinafine 250 mg tablets
Terbinafine Aurobindo Pharma Limited
Terbinafine 250 mg tablets
Terbinafine Aurobindo Pharma Limited
Terbinafine 250 mg tablets
Terbinafine Aurobindo Pharma Limited
Terbinafine 250 mg tablets
28 tablets

Each tablet contains 250 mg terbinafine (as terbinafine hydrochloride).

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store in the original package in order to protect from light.

Use as directed by your doctor.

Marketing Authorisation Holder:
Aurobindo Pharma Limited
Avec, Odyssey Business Park
West End Road
South Rustlip MA4 6QD
United Kingdom
Terbinafine 125 mg tablets

Each tablet contains 125 mg terbinafine (as terbinafine hydrochloride).

Oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Store in the original package in order to protect from light.

Use as directed by your doctor.

Marketing Authorisation Holder:
Aurobindo Pharma Limited
Ares, Odyssey Business Park
West End Road
South Ruislip HA4 6QD
United Kingdom
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the applications for Terbinafine 125 mg tablets and Terbinafine 250 mg tablets for the treatment of fungal infections of the skin and nails caused by dermatophytes, are approvable.

EXECUTIVE SUMMARY

Problem statement
Terbinafine exerts its antimycotic effects by inhibiting fungal sterol biosynthesis to a greater extent than mammalian sterol biosynthesis. Lineweaver-Burke analyses have shown terbinafine to display non-competitive kinetics with fungal squalene epoxidase but competitive kinetics with its mammalian counterpart over a range of squalene concentrations. Moreover, the dissociation constant (Ki) of the fungal enzyme-terbinafine complex is three orders of magnitude lower than for corresponding mammalian complexes. Therefore, the greater sensitivity of fungal than mammalian squalene epoxidase for terbinafine accounts for the allylamine's selective toxicity.

The consequences of squalene epoxidase inhibition are 2-fold. The effect of terbinafine induced ergosterol depletion from fungal cell membranes is fungistatic. A more dramatic consequence of squalene epoxidase inhibition is the intracellular accumulation of its substrate, squalene, which exerts a fungicidal effect by perturbing phospholipid membranes. Although terbinafine exerts a fungicidal effect against dermatophytes and the yeast C. parapsilosis, only a fungistatic effect is exerted against most strains of C. albicans.

About the product
Terbinafine hydrochloride is a synthetic allylamine derivative. Terbinafine interferes specifically with fungal sterol biosynthesis at an early stage. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death.

General comments on the submitted dossier
These abridged decentralised applications concern generic versions of terbinafine (125 mg & 250 mg tablets) submitted under Article 10.1. The originator products are Lamisil 125 mg & 250 mg tablets, respectively, marketed by Novartis Pharma B.V. and first authorised in the EEA in the Netherlands on the 5 December 1991. The legal basis is satisfactory.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been initially 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. 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 of satisfactory inspection summary reports issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-
Community sites.

The Applicant has stated that the bioequivalence study submitted in support of the dossier was conducted in accordance with the principles enunciated in the Declaration of Helsinki and ICH-GCP. Quality assurance certificates relating to the biostatistical report, clinical study report and bioanalytical method validation and data analysis have been provided.

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance
The chemical–pharmaceutical documentation and quality overall summary in relation to Terbinafine 125 mg tablets and Terbinafine 250 mg tablets are of sufficient quality in view of the present European regulatory requirements.

The active substance, terbinafine hydrochloride, is sourced from a manufacturer for which a satisfactory QP declaration which complies with the requirements of Article 46(f) of Directive 2001/83/EC, as amended has been provided.

Terbinafine hydrochloride is the subject of a Ph Eur monograph. The drug substance used in this product has a valid Certificate of Suitability which has been accepted for use.

The control tests and specifications for terbinafine hydrochloride are adequately drawn up.

Stability studies have been performed with the drug substance. No significant changes in any of the parameters were observed for terbinafine hydrochloride stored in ICH conditions. Based on this information, the proposed retest period of 36 months is considered justified.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients are well known and are of pharmacopoeial quality.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on product batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 2 years with the associated storage statement ‘Store in the original package in order to protect from light.’ for both drug products is considered acceptable.

NON CLINICAL ASPECTS
No new non-clinical data have been provided. The pharmacodynamics, pharmacokinetics and toxicology of terbinafine are well established and the non-clinical dossier is based on a review of published literature.
CLINICAL ASPECTS

Pharmacokinetics
To support the application, the applicant has submitted as single bioequivalence study report.

No other novel pharmacokinetic (PK) data are supplied. The PK claims within the SPC are appropriately consistent with the innovator SPC.

Study design
The study was of standard design, i.e., open label, randomized, two-treatment, two-sequence, two-period, cross-over, and single-dose.

Single 250 mg tablet doses of test and reference products were administered to 48 (+ two standby) healthy, adult male subjects aged 18 – 50 years under fasting conditions.

Test and reference products
Test: Terbinafine hydrochloride 250 mg tablets, Aurobindo Pharma Ltd
Reference: Lamisil 250 mg tablets, Sandoz Pharmaceuticals

Terbinafine was measured in plasma by a validated mass spectrometric detection method:

Pharmacokinetic parameters, including $T_{\text{max}}$, $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ and $t_{1/2}$, were calculated from the plasma terbinafine concentrations by non-compartmental analysis using WinNonlin software Version 5.0.1. PK variables are standard and acceptable.

The 95% confidence intervals for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ test-reference ratios all fulfilled bioequivalence criteria.

**Pharmacokinetic parameters (Ln-transformed values and geometric mean ± SD for AUC and Cmax; $t_{\text{max}}$, median, range; $T_{1/2}$, arithmetic mean)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ ng.hr/ml</th>
<th>$AUC_{0-\infty}$ ng.hr/ml</th>
<th>$C_{\text{max}}$ ng/ml</th>
<th>$t_{\text{max}}$ h</th>
<th>$T_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>6490.77</td>
<td>7085.86</td>
<td>1025.07</td>
<td>2.00 (1.25–5.0)</td>
<td>36.31</td>
</tr>
<tr>
<td>Reference</td>
<td>6320.61</td>
<td>6808.78</td>
<td>1015.44</td>
<td>2.25 (1.0–5.0)</td>
<td>31.56</td>
</tr>
<tr>
<td>*T/R Ratio (90% CI)</td>
<td>102.69% (95.29-110.67)</td>
<td>104.07% (95.47-113.44)</td>
<td>100.95% (91.98-110.79)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intra-subject CV (%)</td>
<td>21.34</td>
<td>22.85</td>
<td>26.72</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*AUC$_{\text{0-t}}$ area under the plasma concentration-time curve from time zero to infinity
*AUC$_{\text{0-\infty}}$ area under the plasma concentration-time curve from time zero to $t$ hours
$C_{\text{max}}$ maximum plasma concentration
$T_{\text{max}}$ time for maximum concentration
$T_{1/2}$ half-life

*ln-transformed values

90% confidence intervals of the test/reference ratios for Ln-transformed $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ fulfilled average bioequivalence criteria and bioequivalence has been adequately demonstrated.
Pharmacodynamics
No novel efficacy or safety data are supplied or required for this application. The PD claims within the SPC are generally consistent with the innovator SPC.

Clinical efficacy
No novel efficacy data are supplied or required for this generic application, thus the efficacy claims within the SPC are appropriately consistent with the innovator SPC.

Clinical safety
No new safety data have been submitted and none are required for this application, thus the safety claims within the SPC are appropriately consistent with the innovator SPC.

BENEFIT RISK ASSESSMENT
The overall risk:benefit for the Terbinafine 125 mg tablets and Terbinafine 250 mg tablets is considered favourable.