ANNEX I.1 - oral terbinafine

Agreed Core Safety Profile
oral terbinafine
4. CLINICAL PARTICULARS

4.2 Posology and method of administration

Additional information on special population

Liver impairment
Terbinafine tablets are not recommended for patients with chronic or active hepatic disease (see section 4.4 Special warnings and precautions for use).

Renal impairment
Use of terbinafine tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Elderly
There is no evidence to suggest that elderly patients require different dosages or experience different side effects than younger patients. When prescribing terbinafine tablets for patients in this age group, the possibility of pre-existing impairment of hepatic or kidney function should be considered (see section 4.4. Special warnings and precautions for use).

Children
Only for products approved in the paediatric population:
In children above 2 years of age, terbinafine tablets have been found to be well tolerated.

4.3 Contraindications

Known hypersensitivity to terbinafine or to any of the excipients of terbinafine tablets.

4.4 Special warnings and precautions for use

Liver function
Terbinafine tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing terbinafine tablets, liver function test should be performed. Hepatotoxicity may occur in patients with and without pre-existing hepatic disease therefore periodic monitoring (after 4-6 weeks of treatment) of liver function test is recommended. Terbinafine should be immediately discontinued in case of elevation of liver function test. Very rare cases of serious hepatic failure (some with a fatal outcome, or requiring hepatic transplant) have been reported in patients treated with terbinafine tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine tablets was uncertain. (see section 4.8 Undesirable effects).

Patients prescribed terbinafine tablets should be warned to report immediately any signs and symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine or pale faeces. Patients with these symptoms should discontinue taking oral terbinafine and the patient's hepatic function should be immediately evaluated.

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

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

**Renal function**

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

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as very rare cases of lupus erythematosus have been reported.

**Other**

Terbinafine 125 mg tablets contain lactose (21 mg/tablet). Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take terbinafine 125 mg tablets.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Effect of other medicinal products on terbinafine**

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

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

Cimetidine decreased the clearance of terbinafine by 33%.

Fluconazole increased the Cmax and AUC of terbinafine by 52% and 69% respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other drugs which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with terbinafine.

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

Rifampicin increased the clearance of terbinafine by 100%.

**Effect of terbinafine on other medicinal products**

According to the results from studies undertaken in vitro and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance of most drugs that are metabolised via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives) with exception of those metabolised through CYP2D6 (see below).

Terbinafine does not interfere with the clearance of antipyrine or digoxin.
Some cases of irregular menstruation have been reported in patients taking terbinafine tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

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

Caffeine
Terbinafine decreased the clearance of caffeine administered intravenously by 19%.

Compounds predominantly metabolised by CYP2D6
In vitro and in vivo studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for compounds predominantly metabolised by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonin reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, especially if they also have a narrow therapeutic window (see 4.4. Special warnings and precautions for use).

Terbinafine decreased the clearance of desipramine by 82%.

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

Terbinafine increased the clearance of ciclosporin by 15%.

4.6 Fertility, pregnancy and lactation

Pregnancy
Foetal toxicity and fertility studies in animals suggest no adverse effects. Since clinical experience in pregnant women is very limited, terbinafine tablets should not be used during pregnancy unless clinical condition of the woman requires treatment with oral terbinafine and the potential benefits for the mother outweigh any potential risks for the foetus.

Lactation
Terbinafine is excreted in breast milk; mothers receiving oral treatment with terbinafine should therefore not breast-feed.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following adverse reactions have been observed in the clinical trials or during post marketing experience.
Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data)

### Table 1

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare:</strong></td>
<td>Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Anaemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare:</strong></td>
<td>Anaphylactoid reaction, angioedema, cutaneous and systemic lupus erythematosus</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Anaphylactic reactions, serum sickness-like reaction</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Very common:</strong></td>
<td>Decreased appetite</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not known:</strong></td>
<td>Anxiety, depression*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common:</strong></td>
<td>Headache</td>
</tr>
<tr>
<td><strong>Uncommon:</strong></td>
<td>Hypogeusia**, ageusia**</td>
</tr>
<tr>
<td><strong>Very rare:</strong></td>
<td>Dizziness, paraesthesia and hypoaeesthesia</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Anosmia</td>
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</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Not known:</strong></td>
<td>Hypoacusis, hearing impaired, tinnitus</td>
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<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
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<tbody>
<tr>
<td><strong>Not known:</strong></td>
<td>Vasculitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>Very common:</strong></td>
<td>Abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea.</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Pancreatitis</td>
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</tbody>
</table>

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<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare:</strong></td>
<td>Hepatic failure, hepatic enzymes increased hepatitis, jaundice, cholestasis</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Very common:</strong></td>
<td>Rash, urticaria</td>
</tr>
<tr>
<td><strong>Very rare:</strong></td>
<td>Erythema multiforme ,Stevens-Johnson syndrome, toxic epidermal necrolysis, acute</td>
</tr>
<tr>
<td></td>
<td>generalized exanthematous pustulosis (AGEP)). Psoriasiform eruptions or exacerbation</td>
</tr>
<tr>
<td></td>
<td>of psoriasis. Alopecia,</td>
</tr>
</tbody>
</table>


### Not known:

Photosensitivity reaction, photodermatosis, photosensitivity allergic reaction and polymorphic light eruption

### Musculoskeletal and connective tissue disorders

**Very common:** Arthralgia, myalgia  
**Not known:** Rhabdomyolysis

### General disorders and administration site conditions

**Very rare:** Fatigue  
**Not known:** Influenza like illness, pyrexia

### Investigations

**Not known:** Blood creatinine phosphokinase increased, weight decreased ***

* Anxiety and depressive symptoms secondary to dysgeusia.  
** Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.  
*** *Weight decreased secondary to hypogeusia.

### 4.9 Overdose

A few cases of overdosage (up to 5 g) have been reported, giving rise to headache, nausea, upper abdominal pain and dizziness. The recommended treatment of overdosage consists of eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy, if needed.
4.3 Contraindications

*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder, film forming solution (Once)*

Hypersensitivity to terbinafine or to any of the excipients (see section 6.1.).

4.4 Special warnings and precautions for use

*Gel (Dermgel), solution, spray, continuous spray, spray powder, film forming solution (Once)*

Terbinafine Dermgel / solution / spray / continuous spray / spray powder / Once should be used with caution in patients with lesions where alcohol could be irritating.
It should not be used on the face.  
*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder, film forming solution (Once)*

Terbinafine cream / Dermgel / solution / spray / continuous spray / spray powder / Once is for external use only.

It may be irritating to the eyes. In case of accidental contact with the eyes, rinse eyes thoroughly with running water.

Terbinafine cream / Dermgel / solution / spray / continuous spray / spray powder / Once should be kept out of the reach of children.

*Spray, continuous spray, spray powder*

In case of accidental inhalation, consult a physician if any symptoms develop or persist.

*Film forming solution (Once)*

Terbinafine Once is not recommended to treat hyperkeratotic chronic plantar tinea pedis (moccasin type).

In the event of allergic reaction, the film should be removed with an organic solvent such as denatured alcohol and the feet washed with warm soapy water.

**Information concerning excipients**

**Lamisil cream contains:**
- cetyl alcohol and stearyl alcohol, which may cause local skin reactions (e.g. contact dermatitis).

**Lamisil gel (DermGel) contains:**
- butylhydroxytoluene (E321), which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

**Lamisil solution contains:**
- propylene glycol, which may cause skin irritation.

**Lamisil spray contains:**
- propylene glycol, which may cause skin irritation.

**Lamisil continuous spray contains:**
- propylene glycol, which may cause skin irritation.

**4.5 Interaction with other medicinal products and other forms of interaction**

*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder, film forming solution (Once)*

No drug interactions are known with the topical forms of terbinafine.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder, film forming solution (Once)*

There is no clinical experience with terbinafine in pregnant women. Foetal toxicity studies in animals suggest no adverse effects (see section 5.3).

Terbinafine cream / Dermgel / solution / spray / continuous spray / spray powder / Once should not be used during pregnancy unless clearly necessary.

**Lactation**

*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder*

Terbinafine is excreted in breast milk. terbinafine cream / Dermgel / solution / spray / continuous spray / spray powder should not be used during breast-feeding. In addition, infants must not be allowed to come into contact with any treated skin, including the breast.
Terbinafine is excreted in breast milk. Terbinafine Once should not be used during breast-feeding.

**Fertility**

*For terbinafine topical formulations*

No effect of terbinafine on fertility have been seen in animal studies (see section 5.3).

### 4.7 Effects on ability to drive and use machines

*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder, film forming solution (Once)*

Terbinafine cream / Dermgel / solution / spray / continuous spray / spray powder / Once has no influence on the ability to drive and use machines.

### 4.8 Undesirable effects

*Cream, Gel (Dermgel), solution, spray, continuous spray*

Local symptoms such as pruritus, skin exfoliation, application site pain, application site irritation, pigmentation disorder, skin burning sensation, erythema, scab, etc. may occur at the site of application. These harmless symptoms must be distinguished from hypersensitivity reactions incl. rash, which are reported in sporadic cases and require discontinuation of therapy. In case of accidental contact with the eyes terbinafine may be irritating to the eyes. In rare cases the underlying fungal infection may be aggravated.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: *very common* ($\geq 1/10$); *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* ($< 1/10,000$), or *not known* (can not to be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

#### Immune system disorders

Not known  Hypersensitivity*

#### Eye disorders

Rare  Eye irritation

#### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Skin exfoliation, pruritus</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Skin lesion, scab, skin disorder, pigmentation disorder, erythema, skin burning sensation</td>
</tr>
<tr>
<td>Rare</td>
<td>Dry skin, dermatitis contact, eczema</td>
</tr>
<tr>
<td>Unknown</td>
<td>Rash*</td>
</tr>
</tbody>
</table>

#### General disorders and administration site conditions

Uncommon Pain, application site pain, application site irritation

Rare  Condition aggravated

*: Based on post-marketing experience

#### spray powder

Redness, itching or stinging may occur at the site of application; however, treatment rarely has to be discontinued for this reason. These harmless symptoms must be distinguished from allergic reactions such as pruritus, rash, bullous eruptions and hives, which are rare but require discontinuation.
**Film forming solution (Once)**
Undesirable effects include mild and transient reactions at the site of application. In very rare instances, allergic reactions may occur.

**Skin and subcutaneous tissue disorders:**
Very rare (<1/10,000, including isolated reports):
allergic reactions such as rash, pruritus, dermatitis bullous and urticaria.

**General disorders and administration site conditions**
Uncommon (>1/1,000, <1/100):
application site reactions such as skin dryness, skin irritation or burning sensation.

### 4.9 Overdose
*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder*
The low systemic absorption of topical terbinafine renders overdosage extremely unlikely.

**Cream**
Accidental ingestion of one 30 g tube of terbinafine cream, which contains 300 mg terbinafine hydrochloride, is comparable to ingestion of one terbinafine 250 mg tablet (adult oral unit dose).

**Gel (Dermgel)**
Accidental ingestion of one 30 g tube of terbinafine Dermgel, which contains 300 mg terbinafine base, is comparable to ingestion of one terbinafine 250 mg tablet (adult oral unit dose).

**Solution, spray**
Accidental ingestion of the contents of one 30 ml bottle of terbinafine solution / spray, which contains 300 mg terbinafine hydrochloride, is comparable to ingestion of one terbinafine 250 mg tablet (adult oral unit dose).

**Continuous spray**
Accidental ingestion of the contents of one can of 30 ml of terbinafine continuous spray, which contains 300 mg terbinafine hydrochloride, is comparable to ingestion of one terbinafine 250 mg tablet (adult oral unit dose).

**OR**
Accidental ingestion of the content of one 125 ml bottle of terbinafine continuous spray, which contains 1250 mg terbinafine hydrochloride, is comparable to ingestion of five terbinafine 250 mg tablet (adult oral unit dose).

**Spray powder**
Accidental ingestion of the content of 20 ml of terbinafine spray powder, which contains 180 mg terbinafine hydrochloride, is less than one terbinafine 250 mg tablet (adult oral unit dose).

*Cream, gel (Dermgel), solution, spray, continuous spray, spray powder*
Should a larger amount of terbinafine cream, Dermgel, solution, spray, continuous spray or spray powder be inadvertently ingested, adverse effects similar to those observed with an overdosage of terbinafine tablets are to be expected. These include headache, nausea, epigastric pain and dizziness.

**Solution, spray, continuous spray**
In case of accidental oral ingestion, the alcohol content (28.87% v/v) of terbinafine solution / spray / continuous spray has to be considered.

**Spray powder**
In case of accidental oral ingestion, the alcohol content (57.8% w/w of the concentrate) of terbinafine spray powder has to be considered.

**Gel (dermgel)**
In case of accidental oral ingestion, the alcohol content (9.4% w/w) of terbinafine gel (DermGel) has to be considered.

*Film forming solution (Once)*
In case of accidental oral ingestion, the alcohol content (81.05% w/w) of terbinafine Film forming solution (Once) has to be considered.
**Film forming solution (Once)**

Overdose is very unlikely to happen since the product is for single dose, cutaneous use, and the tube only contains the necessary quantity for one application.

Accidental ingestion of one 4 g tube of product which contains 40 mg terbinafine is much lower than one 250 mg terbinafine tablet (adult oral unit dose).

Should several tubes be of terbinafine Once be inadvertently ingested however, adverse effects similar to those observed with an overdosage of terbinafine tablets are to be expected. These include headache, nausea, epigastric pain and dizziness.

**Cream, gel (Dermgel), solution, spray, continuous spray, spray powder, film forming solution (Once)**

**Treatment of overdose**

If accidentally ingested, the recommended treatment of overdosage consists of eliminating the active substance, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if needed.