SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Terbinafine 250 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg terbinafine (as hydrochloride).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White to off white capsule shaped, biconvex tablets scored on one side and debossed "T" on each side of the score.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Treatment of terbinafine sensitive fungal infections such as Tinea corporis, Tinea cruris and Tinea pedis (caused by Dematophytes see section 5.1) is considered appropriate due to the site, severity or extent of the infection.

2. The treatment of onychomycosis (terbinafine-sensitive fungal infection of the nails) caused by dermatophytes.

N.B. Orally administered terbinafine tablets are not effective against Pityriasis versicolor.
Consideration should be given to official guidance on the appropriate use of antifungal agents.

4.2 Posology and method of administration

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

**Adults**
250 mg once daily.

**Skin infections**
Likely durations of treatment are as follows:

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

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

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

Additional information on special population

**Liver impairment**
Terbinafine 250 mg tablets are not recommended for patients with chronic or active hepatic disease (see section 4.4)

**Renal impairment**
Use of Terbinafine 250 mg tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section 4.4 and section 5.2).

**Elderly**
There is no evidence to suggest that elderly patients require different dosages or experience different side effects than younger patients. When prescribing Terbinafine 250 mg 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).

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

Method of administration
Via the oral route
4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 **Special warnings and precautions for use**

**Liver Function**

Terbinafine is not recommended for patients with chronic or active hepatic disease.

Before prescribing terbinafine, 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. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of terbinafine was uncertain (see section 4.8).

Patients prescribed terbinafine should be warned to report immediately any signs and symptoms of pruritus, 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.

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

**Dermatological effects**

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

**Haematological effects**

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

**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 has not been adequately studied, and therefore, is not recommended (see section 5.2).

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

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 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 $C_{\text{max}}$ 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 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 (TCA's), 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 section 4.4).

Terbinafine decreased the clearance of desipramine by 82%.

Terbinafine may decrease the effect or plasma concentration of the following medicinal products:
Terbinafine increased the clearance of ciclosporin by 15%.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Since clinical experience in pregnant women is very limited, terbinafine 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.

Breastfeeding
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 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 headings of frequency, the most frequent first, using the following convention: very common (≥1/10); 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).
<p>| Table 1 |
|-----------------|------------------|
| <strong>Blood and lymphatic system disorders</strong> | |
| <strong>Very rare:</strong> | Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia |
| <strong>Not known:</strong> | Anaemia |
| <strong>Immune system disorders</strong> | |
| <strong>Very rare:</strong> | Anaphylactoid reactions, angioedema, cutaneous and systemic lupus erythematosus |
| <strong>Not known:</strong> | Anaphylactic reactions, serum sickness-like reaction |
| <strong>Metabolism and nutrition disorders</strong> | |
| <strong>Very common:</strong> | Decreased appetite |
| <strong>Psychiatric disorders</strong> | |
| <strong>Not known:</strong> | Anxiety, depression* |
| <strong>Nervous system disorders</strong> | |
| <strong>Common:</strong> | Headache |
| <strong>Uncommon:</strong> | Hypogeusia**, ageusia** |
| <strong>Very rare:</strong> | Dizziness, paraesthesia, hypoaesthesia |
| <strong>Not known:</strong> | Anosmia |
| <strong>Ear and labyrinth disorders</strong> | |
| <strong>Very rare:</strong> | Vertigo |
| <strong>Not known:</strong> | Hypoacusis, hearing impaired, tinnitus |
| <strong>Vascular disorders</strong> | |
| <strong>Not known:</strong> | Vasculitis |
| <strong>Gastrointestinal disorders</strong> | |
| <strong>Very common:</strong> | Abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea, feeling of fullness, loss of appetite |
| <strong>Not known:</strong> | Pancreatitis |
| <strong>Hepatobiliary disorders</strong> | |
| <strong>Rare:</strong> | Cases of serious hepatic failure If hepatic dysfunction develops, treatment with terbinafine should be discontinued (see also section 4.4). Hepatic enzymes increased |</p>
<table>
<thead>
<tr>
<th>Not known:</th>
<th>Hepatitis, jaundice, cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common:</strong></td>
<td>Non-serious forms of skin reactions (rash, urticaria)</td>
</tr>
<tr>
<td><strong>Very rare:</strong></td>
<td>Serious skin reactions: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP). Psoriasiform eruptions or exacerbation of psoriasis. If progressive skin rash occurs, terbinafine treatment should be discontinued. Alopecia</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Photosensitivity reaction, photodermatitis, photosensitivity allergic reaction and polymorphic light eruption</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common:</strong></td>
<td>Arthralgia, myalgia</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare:</strong></td>
<td>Menstruation irregular Breakthrough bleeding (LLT)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rare:</strong></td>
<td>Malaise</td>
</tr>
<tr>
<td><strong>Very rare:</strong></td>
<td>Fatigue</td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Influenza like illness, pyrexia</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Not known:</strong></td>
<td>Blood creatinine phosphokinase increased, weight decreased ***</td>
</tr>
</tbody>
</table>

* 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.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.
4.9  Overdose

Symptoms
A few cases of overdosage (up to 5 g) have been reported, giving rise to headache, nausea, upper abdominal pain and dizziness.

Treatment of overdose
The recommended treatment of overdosage 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; antifungals for systemic use
ATC code: D01B A 02

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

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system.

When given orally, the active substance concentrates in skin at levels associated with fungicidal activity.

5.2  Pharmacokinetic properties

Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine from terbinafine tablets as a result of firstpass metabolism is approximately 50 %. A single oral dose of 250 mg terbinafine resulted in mean peak plasma concentrations of 1.30 µg/ml within 1.5 hours after administration. At steady-state, in comparison to a single dose, peak concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3. From the increase in plasma AUC an effective half-life of ~30 hours can be calculated. The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20%), but not sufficiently to require dose adjustments. Terbinafine binds strongly to plasma proteins. It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum.
Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum rich skins. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks of commencing therapy. Terbinafine is metabolised rapidly and extensively by at least seven CYP isoenzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity, which are excreted predominantly in the urine.

No clinically-relevant 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.

Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance <50ml/min) or with pre-existing liver disease have shown that clearance of terbinafine may be reduced by about 50%.

5.3 Preclinical safety data

In long-term studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the blister in the outer carton.

6.5 Nature and contents of container

PVC/Aluminium blister or PVC/PVDC/Aluminium blister: 8, 14, 28, 30, 42, 50, 56 and 98 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH
Graf-Arco-Strasse 3
D-89079 Ulm
Germany

8. MARKETING AUTHORISATION NUMBER(S)
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/04/2009

10 DATE OF REVISION OF THE TEXT
03/01/2017