Summary of Product Characteristics

Terbinafine Rowa 250 mg Tablets

1 NAME OF THE MEDICINAL PRODUCT

Terbinafine Rowa 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets for oral administration.
White oblong tablets scored on both sides.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Treatment of Terbinafine sensitive fungal infections in adults, 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 in adults (terbinafine-sensitive fungal infection of the nails) caused by dermatophytes.

Due consideration should be given to national guidance concerning the correct usage and prescription of anti-fungal agents.

4.2 Posology and method of administration

Posology
Adults: 250 mg (1 tablet) once daily.
The duration of treatment varies according to the indication and the severity of the infection.

Skin infections
Likely durations of treatment are as follows:
Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks
Tinea corporis: 4 weeks
Tinea cruris: 2 to 4 weeks

It can take a number of weeks after mycological healing before the complaints and signs of the infection have disappeared completely.

Onychomycosis
The duration of treatment for most patients is between 6 weeks and 3 months. Treatment periods of less than 3 months can be anticipated in patients with fingernail infection, toenail infection other than of the big toe, or patients of younger age. In the treatment of toenail infections, 3 months is usually sufficient although a few patients may require treatment of 6 months or longer.
Poor nail outgrowth during the first weeks of treatment may enable identification of those patients in whom longer therapy is required.
Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure and termination of the therapy. This depends on the time the healthy nail needs to grow.

Additional information on special population

Liver impairment
Terbinafine tablets are contraindicated in patients with chronic or active hepatic disease (see sections 4.3 and 4.4).

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 sections 4.4 and 5.2).

Elderly
There is no evidence to suggest that elderly patients (aged 65 years or above) 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 in this age group (see section 4.4.).

Paediatric Population
Terbinafine 250 mg tablets is not recommended in children and adolescents (<18 years) due to lack of experience in this age group.

Method ofadministration
The scored tablets are taken orally with water. They should preferably be taken at the same time each day and can be taken on any empty stomach or after a meal.

4.3 Contraindications

Hypersensitivity to active substance or to any of the excipients of terbinafine tablets listed in section 6.1.
Severe hepatic impairment.

4.4 Special warnings and precautions for use

Liverfunction
Terbinafine tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing terbinafine tablets, liver function test should be performed and any pre-existing liver disease should be assessed.

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 liver 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).

Patients prescribed terbinafine tablets should be instructed to report immediately any signs and symptoms suggestive of liver dysfunction, such as pruritus, unexplained persistent nausea, decreased appetite, anorexia, jaundice, vomiting 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 liver function should be immediately evaluated.

Dermatological effects
Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms) have been very rarely reported in patients taking terbinafine tablets. If progressive skin rash occurs, terbinafine tablets treatment should be discontinued (see section 4.8).

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

Renal function

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

Psoriasis/lupus erythematosus
Terbinafine tablets should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as there have been post-marketing reports of occurrences or deterioration of psoriasis or cutaneous/systemic lupus erythematosus.

Excipient(s) with known effect
Terbinafine tablets contain less than 1 mmol sodium (23 mg) per tablet, i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interactions

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 C_{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

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
Invitro and *invivo* 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 section 4.4.).

Terbinafine decreased the clearance of desipramine by 82%.

In studies in healthy subjects characterized as extensive metabolisers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16- to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolisers (genotype) to poor metaboliser (phenotype) status.

Information on other drug concomitantly used with Terbinafine Rowa resulting in no or negligible interactions.

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 above).

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

There was no effect of terbinafine on the pharmacokinetics of fluconazole. Further there was no clinically relevant interaction between terbinafine and the potential comedications cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual disturbance (breakthrough bleeding and irregular cycle) 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 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
Foetal toxicity and fertility studies in animals suggest no adverse effects (see section 5.3). 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 and therefore mothers should not receive Terbinafine Rowa 250 mg Tablets treatment whilst breast-feeding.

Fertility
Foetal toxicity and fertility studies in animals suggest no adverse effects (see section 5.3).

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)

Table1

Bloodandlymphaticsystemdisorders
Veryrare: Neutropenia, agranulocytosis, thrombocytopenia, *Notknown:* Anaemia, pancytopenia
Immunesystemdisorders
Very rare: Anaphylactoid reaction (including angioedema), cutaneous and systemic lupus erythematosus *Notknown:* Anaphylactic reactions, serum sickness-like reaction
Metabolismandnutritiondisorders
Verycommon: Decreased appetite
Psychiatricdisorders
Notknown: Anxiety, depression*
Nervoussystemdisorders
Common: Headache

Uncommon: Ageusia**, hypogeusia**, dysgeusia**
Eye disorders *Common:* Visual impairment *Not known:* Visual blurred, visual acuity reduced
Earandlabyrinthdisorders
Very rare: Vertigo *Notknown:* Hypoacusis, hearing impaired, tinnitus
Vasculardisorders
Notknown: Vasculitis
Gastrointestinaldisorders
Verycommon: Feeling of fullness,abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea. *Notknown:* Pancreatitis
Hepatobiliarydisorders
Rare: Cases of serious hepatic dysfunction, including hepatic failure, hepatic enzymes increased, jaundice, cholestasis and hepatitis. If hepatic dysfunction develops, treatment with Terbinafine tablets should be discontinued (see also Section 4.4). Very rare cases of serious liver failure have been reported (some with a fatal outcome, or requiring liver transplant). In the majority of liver failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Terbinafine Rowa was uncertain.
Skinandsubcutaneoustissuedisorders
Verycommon: Rash, urticaria *Veryrare:* Stevens- Johnson syndrome, toxic epidermal necrolysis, erythema multiforme toxic skin eruption, dermatitis exfoliative, dermatitis bullous, Photosensitivity reactions. Alopecia If progressive skin rash occurs, Terbinafine Rowa treatment should be discontinued. *Notknown:* Psoriasiform eruptions or exacerbation of psoriasis. Serious skin reactions (e.g. acute generalized exanthematous pustulosis (AGEP)). Drug rash with eosinophilia and systemic symptoms
Musculoskeletalandconnectivetissuedisorders
Verycommon: Musculoskeletal reactions (Arthralgia, myalgia) *Notknown* Rhabdomyolysis
Generaldisordersandadministrationsiteconditions
Rare: Malaise *Veryrare:* Fatigue *Notknown:* Influenza like illness, pyrexia
Investigations
Uncommon: Weight decreased*** *Notknown:* Blood creatinine phosphokinase increased

*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.

Reportingofsuspectedadversereactions
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 HPRA Pharmacovigilance, website: www.hpra.ie

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antifungals for systemic use, ATC Code: *D01B A02*.

Terbinafine is an allylamine which has a broad spectrum of 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 stage. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibiting squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system.

When given orally, the drug concentrates in the skin, hair and nails at levels associated with fungicidal activity.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, terbinafine is well absorbed (>70%) and the absolute bioavailability of terbinafine from terbinafine tablets as a result of first-pass metabolism is approximately 50%. A single oral dose of 250mg terbinafine resulted in mean peak plasma concentrations of 1.30 micorgrams/ml within 1.5 hours after administration. Plasma concentrations decline in a triphasic manor, with a terminal half-life of 16.5 days. At 28 days, when around 70% steady state levels have been achieved, peak concentrations of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3 when compared to single dose administration. 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.

Distribution
Terbinafine binds strongly to plasma proteins. It rapidly diffuses through the dermis and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum rich skins. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks of commencing therapy.

Biotransformation
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 <50 ml/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, for oral doses of up to 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 obtained for doses of up to 130 mg/kg a day (males) and 156 mg/kg a day (females). In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumours was observed in males at the highest dose 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 observed in the carcinogenicity study in mice or in other studies in mice, dogs or monkeys.

During terbinafine high-dose studies in monkeys, refractive irregularities were observed in the retina at the higher doses (non-toxic effect level was 50 mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after treatment 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 of the drug.

No adverse effects on fertility or on other reproduction parameters were observed in studies in rats or rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Starch Glycolate (type A)
Cellulose Microcrystalline (E460)
Hypromellose (E464)
Silica Colloidal Anhydrous
Magnesium Stearate (E572)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

No special requirements

6.5 Nature and contents of container

Transparent PVC/Aluminium or PVC-PVDC/Aluminium blister pack.
Packs of 14, 28 and 98 tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

This medicinal product does not require any special storage conditions.

7 MARKETING AUTHORISATION HOLDER

Rowa Pharmaceuticals Limited
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0074/084/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisaton: 12 January 2007
Date of last renewal: 4 February 2010

10 DATE OF REVISION OF THE TEXT

July 2022