SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Azurifin 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg terbinafine, as terbinafine hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, flat, 11 mm tablets, scored on both sides with side scores, marked “T” above and “1” below the score on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- 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.

- 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.
The official local guidelines should be borne in mind, for example, national recommendations relating to the correct use and prescription of antimicrobial drugs”.

4.2 Posology and Method of Administration

Posology

Adults:
250mg once daily.

Renal impairment
Use of Azurifin 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).

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

Skin infections

The likely durations of treatment for Tinea pedis, Tinea corporis and Tinea cruris are 2 – 4 weeks.
For Tinea pedis (interdigital, plantar/moccasin-type): recommended treatment periods may be up to 6 weeks.
Complete disappearance of the symptoms of the infection may not occur until several weeks after mycological cure.

Onychomycosis
In most patients the duration of successful treatment is 6-12 weeks.
Fingernail onychomycosis: In most cases 6 weeks' treatment is sufficient in fingernail onychomycosis.
Toenail onychomycosis: In most cases 12 weeks' treatment is sufficient in toenail onychomycosis although a few patients may require treatment up to 6 months. 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 is only seen several months after stopping treatment, which is the time for growth of a healthy nail.

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

Method of administration

Oral use

The duration of treatment is dependent on the indication and the degree of severity of the infection.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Terbinafine is a potent inhibitor of the isoenzyme CYP2D6, which should be considered if Azurifin is combined with medicinal products metabolised by this isoenzyme that are titrated individually (see section 4.5). Dose adjustments may be necessary.

Should be used with caution for patients with renal impairment (see 4.2 and 4.3).

Liver function
Azurifin tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing Azurifin 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. Azurifin 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 Azurifin tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Azurifin tablets was uncertain. (see sections 4.3 Contraindications and 4.8 Undesirable effects).

Patients prescribed Azurifin 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 Azurifin and the patient's hepatic function should be immediately evaluated.

In patients with liver disease, pharmacokinetic studies show that clearance can be reduced by approximately 50%.

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 Azurifin tablets. If progressive skin rash occurs, Azurifin treatment should be discontinued.

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

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

Patients on terbinafine who develop a high fever or sore throat should be examined concerning possible haematological reactions.

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 Azurifin tablets has not been adequately studied, and therefore, is not recommended (see section 5.2 Pharmacokinetic properties).

Excipients with known effect
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Azurifin

The plasma clearance of terbinafine may be accelerated by drugs which induce metabolism (such as rifampicin) and may be inhibited by drugs which inhibit cytochrome P450 (such as cimetidine). Where co-administration of such drugs is required, it may be necessary to adjust the dose of terbinafine accordingly.

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

Cimetidine decreased the clearance of Azurifin by 33%.

A single dose of 100 mg luconazole increased the Cmax and AUC of Azurifin 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 Azurifin. Therefore, it may be necessary to adjust the dose of Azurifin tablets when co-administration of such drugs.

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

Rifampicin increased the clearance of Azurifin by 100%.

Therefore, it may be necessary to adjust the dose of Azurifin tablets when co-administration of such drugs.

Effect of Azurifin on other medicinal products
According to the results from studies undertaken in vitro and in healthy volunteers, Azurifin 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).

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

No clinically relevant interaction was observed between single doses of terbinafine and the potentially concomitant treatment of cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of irregular menstruation have been reported in patients taking Azurifin tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

Terbinafine does not affect the metabolism of hormones.

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

Caffeine
Some inhibition of the enzyme CYP1A2 has been observed *in vitro.* Azurifin decreased the clearance of caffeine administered intravenously by 19%.

Compounds predominantly metabolised by CYP2D6
In vitro and in vivo studies have shown that Azurifin 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 serotonine 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).

Azurifin 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 up to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolisers (genotype) to poor metaboliser status (phenotype).

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

Azurifin increased the clearance of ciclosporin by 15%.

4.6 Pregnancy and lactation

Pregnancy

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

Breast-feeding
Azurifin is excreted in breast milk; mothers receiving oral treatment with Azurifin 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 Azurifin 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.

In clinical trials, up to 10% have experienced side effects.
The side effects are usually short-lived. Gastrointestinal disorders are the most common (5%).

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

Blood and lymphatic system disorders	
Uncommon:	Anaemia
Very rare:	Neutropenia, agranulocytosis, thrombocytopenia (frequency <0,02%), pancytopenia
Immune system disorders	
Very rare:	Anaphylactoid reaction, angioedema, cutaneous and systemic lupus erythematosus
Not known:	Anaphylactic reactions, serum sickness-like reaction
Metabolism and nutrition disorders	
Very common:	Decreased appetite
Psychiatric disorders	
Common:	Depression*
Uncommon:	Anxiety*
Nervous system disorders	
Very common:	Headache

Common:	Hypogeusia**, ageusia**, dizziness
Uncommon:	Paraesthesia and hypoaesthesia Malaise
Rare:	
Not known:	Anosmia
Eye disorders	
Common:	Visual impairment
Not known:	Vision blurred, visual acuity reduced
Ear and labyrinth disorders	
Uncommon:	Tinnitus
Not known:	Hypoacusis, hearing impaired
Vascular disorders	
Not known:	Vasculitis
Gastrointestinal disorders	
Very common:	Bloated feeling, abdominal distension, dyspepsia, nausea, abdominal pain, diarrhoea.
Not known:	Pancreatitis
Hepatobiliary disorders	
Rare:	Hepatic failure, hepatic enzymes increased
Not known:	hepatitis, jaundice, cholestasis
Skin and subcutaneous tissue disorders	
Very common:	Rash, urticaria
Uncommon:	Photosensitivity reaction
Very rare:	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP), toxic skin eruption, dermatitis exfoliative, dermatitis bullous Psoriasiform eruptions or exacerbation of psoriasis Alopecia
Not known:	Drug rash with eosinophilia and systemic symptoms, 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	
Common:	Fatigue
Uncommon:	Pyrexia
Not known:	Influenza like illness
Investigations	
Uncommon:	Weight decreased ***
Not known:	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.

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 national reporting system listed in Appendix V.

4.9 Overdose

Few cases of overdose (up to 5g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness. Recommended treatment for overdose consists of eliminating the active substance, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dermatologicals; antifungals for systemic use, ATC code: D01B A02

Mechanism of Action
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 selectively with fungal sterol biosynthesis at an early stage through inhibition of the enzyme squalene epoxidase. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene in the fungal cell membrane. Both the deficiency in ergosterol and the accumulation of squalene are responsible for fungal cell death.

When given orally, the active substance concentrates in skin, hair and nails at levels associated with fungicidal activity. Measurable concentrations of the active substance are still evident 15 – 20 days after cessation of treatment.

Terbinafine is used for the treatment of fungal infections of the skin and nails, which is caused by Trichophyton (e.g.T. rubrum, T.mentagrophytes, T. verrucosum, T. violaceum), Microsporum canis and Epidermophyton floccosum. The following table outlines the range of minimum inhibitory concentrations (MIC) against the dermatophytes.

Organism	MIC rang (µg/ml)
Trichophyton rubrun	0.001 – 0.15
Trichophyton mentagrophytes	0.0001 – 0.05
Trichophyton verrucosum	0.001 – 0.006
Trichophyton violaceum	0.001 – 0.1
Microsporum canis	0.0001 – 0.1
Edidermorphyton fluccosum	0.001 – 0.05

Terbinafine exhibits poor efficacy against many yeasts of the Candida species.

Terbinafine tablets in contrast to locally administered terbinafine treatment, has no effect in the treatment of Pityriasis (Tinea) versicolor.

5.2 Pharmacokinetic properties

Absorption
A single oral dose of 250mg terbinafine results in mean peak plasma concentrations of 0.97 µg/ml within 2 hours after administration. The absorption half-life is 0.8 hours and the distribution half-life is 4.6 hours. The bioavailability of terbinafine is only slightly affected by food with an increase about 16%, and therefore a dose adjustment is not necessary.

Distribution
Terbinafine binds strongly to plasma proteins (99%).
Terbinafine rapidly diffuses through the skin and concentrates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and parts of the skin rich in sebaceous glands. There is also evidence that terbinafine is distributed into the nail plate within a few weeks after commencing therapy.

Biotransformation
Terbinafine is rapidly metabolised by the CYP-isoenzymes, mainly by CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity.

Elimination
Metabolites are excreted predominantly in the urine.
At steady state, the AUC is about 2.3 times higher than after a single dose. Based on the increase in AUC, the effective half-life is about 30 hours.
Terbinafine exhibits a three-phase elimination with a terminal half-life of approximately 16.5 days.

Other special populations
Preliminary data show markedly elevated plasma levels, so Azurifin should not be given to patients with severe renal or hepatic impairment until further data are available. In patients with pre-existing mild to severe hepatic impairment, single dose pharmacokinetic studies have shown that the clearance of terbinafine can be reduced by 50%."

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.

5.3 Preclinical safety data

The approximate LD_{50} value of terbinafine is over 4 g/kg in both mice and rats.

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

In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumours was observed in males at the highest dosage level of 69 mg/kg, at which systemic exposure was similar to clinical exposure. The mechanism of tumour development has not been established. The clinical relevance is unknown. The changes which may be associated with peroxisome proliferation have been shown to be species-specific since they were not seen in the carcinogenicity study in mice, dogs or monkeys.

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

Magnesium stearate
Silica, colloidal anhydrous
Croscarmellose sodium
Hypromellose
Microcrystalline cellulose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Al/PVC-PVdC blister
3 years

HDPE tablet container with LDPE cap
18 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/PVC-PVdC blister and HDPE tablet container with LDPE cap

Pack Sizes:
HDPE bottles: 14, 28, 500 tablets
Blisters: 7, 14, 20, 28, 30, 42, 50, 60, 84, 90, 98, 100, 50 x 1 (unit dose) tablets

*Not all container types or pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTORISATION NUMBER

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION

<Date of first authorisation:{DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

2021-06-11