**SUMMARY OF PRODUCT CHARACTERISTICS**

1. **NAME OF THE MEDICINAL PRODUCT**

<TRADE NAME> <STRENGTH> Tablets

<REGARDING THE APPROVAL>

1. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains <GENERIC NAME> <STRENGTH>

<REGARDING THE APPROVAL>

For a full list of excipients, see section 6.1.

1. **PHARMACEUTICAL FORM**

Film-coated tablet.

<REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. **Therapeutic indications**

The treatment of fungal infections of the skin, scalp, hair, or nails (Tinea barbae, Tinea capitis, Tinea corporis, Tinea cruris, Tinea pedis, Tinea unguium) where topical therapy is considered inappropriate, or the infection has proven refractory to topical therapy.

Oral administration of <GENERIC NAME> for systemic therapy of fungal infections enables newly formed keratin of the skin, hair, and nails to resist fungal attack.

As the new keratin extends, the old infected keratin is shed.

# Prior to therapy, the type of fungi responsible should be identified. The use of <GENERIC NAME> is not justified in the treatment of minor or trivial infections that will respond to topical therapy.

# Before prescribing <GENERIC NAME> Tablets, consideration should be given to national and/or local guidance on the appropriate use of antifungals.

## Posology and method of administration

## *General:*

## For oral administration.

## Tablets should be swallowed whole with a glass of water. <GENERIC NAME> is recommended to be taken after a high fat meal, for increased absorption and minimising GI distress, see section 5.2.

## General measures in regard to hygiene should be observed to control sources of infection or reinfection. Concomitant use of appropriate topical agents is usually required, particularly in treatment of tinea pedis. In some forms of tine pedis, yeasts and bacteria may be involved as well as fungi.

## <GENERIC NAME> will not eradicate the bacterial or candidial infections.

## Adults

## The usual adult dose is 500 mg to 1000 mg daily. The dose should not be less than 10 mg / Kg bodyweight / day. The dose may be administered as a single daily dose, or it may be administered twice daily.The twice daily dosing regimen may be more effective in those patients who respond poorly.

## Hepatic impairment

## <GENERIC NAME> is contraindicated in patients with severe hepatic impairment, see section 4.3.

## For patients with moderate to mild hepatic impairment, no dosage adjustment is required. However <GENERIC NAME> may lead to further impairment of hepatic function, therefore regular monitoring of liver function is mandated, see section 4.4.

## Renal impairment

## No dosage adjustment is required in renally impaired patients; renal insufficiency does not lead to accumulation.

## Elderly

## No dosage adjustment is required in the elderly. Consideration should be given that such patients may also have a degree of hepatic impairment, see section 4.4.

## Children

## The dosage form, film-coated tablet, is only suitable for children of an age to swallow the tablet.

## The usual dose in 10 mg / Kg bodyweight / day, in divided doses.

## Duration of therapy

## The duration of theapy depends upon the thickness of keratin at the site of infection, and the clinical response. The following duration of therapy are indicative:

* Tinea corporis: 2-4 weeks
* Tinea capitis: 4-8 weeks, in refractory cases, 8-12 weeks
* Tinea pedis: 4-8 weeks
* Tinea unguium: 6-12 months

Therapy should be continued for at least two weeks after all signs of infection have disappeared.

## Contraindications

## <GENERIC NAME> is contraindicated in patients who have:

* Hypersensitivity to <GENERIC NAME> or to any of the excipients, see section 6.1
* Porphyria
* Severe hepatic impairment
* Systemic Lupus Erythematosus (SLE)
* Pregnancy, see section 4.6
* Breastfeeding, see section 4.6
  1. **Special warnings and precautions for use**

<GENERIC NAME> is reccomended after a high fat meal for increased absorption and minimising GI distress.

<GENERIC NAME> is contraindicated in patients with severe hepatic impairment, see section 4.3. In patients with minor to moderate hepatic impairment, <GENERIC NAME> may cause further deterioration of hepatic function. Therefore care should be exercised with such patients, and it is recommended to perform regular periodic liver function tests, see section 4.8.

<GENERIC NAME> is contraindicated in patients with Systemic Lupus Erythematosus (SLE), see section 4.3; <GENERIC NAME> has been reported to exacerbate the conditions, and care should be taken to exclude patients with pre-existing SLE from therapy.

Animal data, see section 5.3, indicates long term administration of high dose <GENERIC NAME> induces tumours in some species, but not others. The clinical relevance of this to man is unknown, but <GENERIC NAME> should not be used prophylactically.

<GENERIC NAME> is a liver microsomal enzyme inducer and thus may impair the effectiveness of oral contraceptives. Therefore in women of child bearing age using oral contraception, additional barrier methods of contraception must be used during therapy and for 4 weeks following therapy cessation, see sections 4.5 and 4.6.

<GENERIC NAME> causes chromosomal abnormalities in animals, see section 5.3. Therefore sexually active males should be cautioned to use an effective barrier method of contraception throughout therapy and for 6 months after therapy termination, see section 4.6.

A theoretical possibility of cross sensitivity in patients known to be allergic to penicillins exists, therefore caution should be exercised in administration of <GENERIC NAME> to such patients. It should be noted that such patients have been satisfactorily treated with <GENERIC NAME> without sequelae.

Patients should be cautioned to avoid excessive and unnecessary exposure to sunlight or U.V sources, including sunbeds, during <GENERIC NAME> therapy as photosensitivity reactions can occur, see section 4.8.

Consumption of alcohol in association with <GENERIC NAME> can result in an “Antabuse” type reaction, see section 4.5. Patients should be cautioned to avoid consumption of alcoholic beverages, and medicines containing alcohol, while undergoing <GENERIC NAME> therapy.

In patients undergoing long term <GENERIC NAME> therapy, i.e for tinea unguium, consideration should be given to periodic monitoring of blood chemistry, particularly for patients with pre-existing blood disorders, since <GENERIC NAME> may cause blood disorders, see section 4.8.

In common with any antibiotic, therapy with <GENERIC NAME> may result in the overgrowth of non-susceptible organisms, i.e bacteria or yeasts, or nondermatophyte fungi, that are often cofactors in tinea infections, especially tinea pedis. Additional therapy is required to control or eradicate such organisms, as <GENERIC NAME> is ineffective.

<GENERIC NAME> is not effective in infections due to *Candida albicans, Aspergillus sp., MMalassezia furfur (Pittyriasis versiclor)* and *Nocardia* sp. It has no antibacterial effects.

* 1. **Interaction with other medicinal products and other forms of interaction**

Medicinal Products:

<GENERIC NAME> may depress plasma levels, and therefore the efficacy, of concommitantly administered medicinal products that are metabolised by cytochrome P450 3A4.

Interactions of <GENERIC NAME> with other drugs:

* *Ciclosporin:* concomittant administration may result in a reduction of ciclosporin plasma levels, necessitating a dosage adjustment. Plasma levels of ciclosporin should be monitored during grisefulvin therapy, and necessary dosage adjustments made.
* *Coumarin anticoagulants:* the efficacy may be reduced, necessitating dosage adjustment. It is recommended that both prothrombin and INR are regularly monitored, for the duration of <GENERIC NAME> therapy, and for 8 days post therapy cessation.

## *Methadone:* depression of methadone plasma levels may occur during <GENERIC NAME> therapy. Patients should be closely monitored for any loss of efficacy, or plasma levels of methadone be monitored, and corresponding dosage adjustments made.

## *Oral contraceptives:* efficacy of oral contraception is reduced during <GENERIC NAME> therapy and for four weeks post therapy cessation. In view of the contraindication in pregnancy, see section 4.3, and of the possible sequelae of male patients fathering a child during therapy, all sexually active patients should use additional barrier contraception, such as condoms, throughout <GENERIC NAME> therapy, and for four weeks (female) and 6 months (male) post therapy cessation. See also sections 4.3, 4.4, 4.6, and 5.3 for additional information.

## Interactions of other drugs with <GENERIC NAME>:

## Concurrent administration of other medicinal products that induce metabolising enzymes may result in a reduction of <GENERIC NAME> blood plasma levels and thus efficacy. The following drugs are known to have this effect:

* *Barbiturates*, such as phenobarbitone
* *Doxercalciferol*
* *Phenylbutazone*
* *Primidone*
* Other sedative and hypnotic drugs that induce metabolising enzymes.
* *Food:* administration of <GENERIC NAME> after food, results in increased absorption, and thus higher plasma levels. This effect is enhanced if the meal contains high fat content. Administration after food is recommended, see section 4.2.
* *Alcohol:* there are reports that <GENERIC NAME> enhances the central nervous system effects of alcohol. There are also reports that <GENERIC NAME> and alcohol use result in an “Antabuse” type reaction. Patients should be cautioned to avoid alcohol and all alcohol containing products while undergoing <GENERIC NAME> therapy, See also section 4.8
  1. **Pregnancy and lactation**

Pregnancy:

There are case reports of human foetal abnormalities associated with <GENERIC NAME>.

There are no adequate and well controlled studies in man, and inadequate epidemiological data. <GENERIC NAME> has been shown to be teratogenic and embryotoxic in mice and rats. (see section 5.3).

<GENERIC NAME> is suspected to cause serious birth defects when administered during pregnancy.

<GENERIC NAME> is contraindicated (see section 4.3) in pregnancy.

Women of childbearing potential have to use effective contraception during (and up to 4 weeks after) treatment (see section 4.5) in respect of effect on oral contraceptives, and contraceptive precautions.

## Male-mediated effects on pregnancy

## <GENERIC NAME> has been shown to induce chromosomal aberrations in animal spermatocytes (see section 5.3).Therefore men should take effective contraceptive precautions, i.e barrier contraception, to avoid fathering children for the duration of <GENERIC NAME> therapy, and for 6 months post therapy cessation.

## Lactation:

## It is unknown if <GENERIC NAME> is excreted in breast milk, but the possibility does exist. There is inadequate data on the safety of <GENERIC NAME> in breast feeding, and the potential risk to the infant cannot be assessed, therefore <GENERIC NAME> is contraindicated in breast feeding (see section 4.3).

## Effects on ability to drive and use machines

## <GENERIC NAME> has no or negligible influence on the ability to drive and use machines. However, it may cause drowsiness, confusion dizziness, and impaired co-ordination, see section 4.8. Patients should therefore be cautioned not to drive or operate machines until they are sure they are not affected.

## Undesirable effects

## The following frequencies are used for the description of the occurrence of undesirable effects:

* 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

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Headache and gastric discomfort are the most common effects on starting treatment, but usually disappear as treatment is continued.

Blood and lymphatic system disorder:

Rare: leucopenia, neutropenia, anaemia-these usually resolve on therapy cessation

Nervous system disorders:

Common: headache

Uncommon: impaired co-ordination, peripheral neuropathy, confusion, dizziness, drowsiness, insomnia, irritability.

Gastrointestinal disorders*:*

Common: diarrhoea, vomiting, nausea, gastric discomfort

Uncommon: anorexia, taste sensation changes

Skin and subcutaneous tissue disorders:

Uncommon: toxic epidermal necrolysis, erethema multiforme, photosensitivity on exposure to intense natural or artifical sunlight.

Rare: precipitation of Systemic Lupus Eryhthematosus, bullous reactions including Lyell’s syndrome, urticarial reactions, skin rashes.

Hepatobiliary disorders:

Very rare: alteration in liver function tests, with elevation to more than three times upper normal limit, intrahepatic cholecstasis, hepatitis.

* 1. **Overdose**

No case of overdose has been reported.

**Symptoms:**

The likely symptoms of any overdose would be nausea, nomiting, headache, numbness and tingling, confusion, and vertigo. Urticaria or porphyria could occur.

**Treatment:**

There is no specific antidote to <GENERIC NAME>. Gastric lavage, or the induction of emesis may be of help, if ingestion is recent. Administration of activated charcoal may also be of use. Treatment should be symptomatic and supportive. Laboratory monitoring of haemopoetic, hepatic and nephritic parameters and electrolytes is recommended.

# PHARMACOLOGICAL PROPERTIES

# Pharmacodynamic properties

# Pharmacotherapeutic group: Antifungals for systemic use

# ATC code: D01BA01

# <GENERIC NAME> is an antifungal antibiotic that is active *in vivo* against common dermatophytes. The antifungal effect is manifested by binding to tubulin, at distinct binding sites, thus interferring with the microtubule function and causing inhibition of mitosis, and arresting cell division. The inhibition of fungal mitosis leads to the production of multinucleate cells of characteristic morphology. On entering the systemic circulation, <GENERIC NAME> binds to keratin in keratin precursor cells, thereby making them resistant to fungal infections. The drug only reaches the site of action when hair or skin is replaced by the keratin<GENERIC NAME> complex.

<GENERIC NAME> then enters the dermatophyte through energy dependent transport processes and binds to the fungal microtubules, interferring with, and inhibiting mitosis, and the deposition of fungal cell walls.

Mycology:

<GENERIC NAME> has antifungal activity against the following dermatophytes, although there is species and strain variability in susceptibility. *Trichophyton rubrum, T. tonsurans, T. mentagrophytes, T. interdigitalis, T. verrucosum, T. megnini, T. gallinae, T. Crateriform, T. sulphureum* and *T.* *schoenleinii*. *Microsporum audouinii, M. Canis, M. gypseum*. *Epidermophyton floccosum*.

<GENERIC NAME> has no activity against dermatophyte fungi of other genera, nondermatophyte fungi, yeasts, gram positive bacteria, or gram negative bacteria. If any of these are cofactors in the pathology of infection, suitable additional therapy will be required for their eradication.

* 1. **Pharmacokinetic properties**

Absorption:

The absorption of <GENERIC NAME> from the gastrointestinal tract is varaible and incomplete. On average, less than 50% of the oral dose is absorbed, but administration after a fatty meal, and a reduction in particle size will increase the rate and extent of the absorption.

Following oral administration there is a phase of rapid absorption, and thereafter a phase of slower prolonged absorption.

Peak plasma levels, 0.5 µg / ml-1.5 µg / ml after a 500 mg dose, and 1.5 µg / ml-3.0 µg / ml after a 1000 mg dose, are reached in 2-4 hours, and are maintained for some 10-20 hours.

<GENERIC NAME> exhibits linear pharmacokinetics.

Distribution:

The volume of distribution is about 0.7 L / Kg, and <GENERIC NAME> is *ca* 80 % bound to plasma proteins, predominantly serum albumin.

<GENERIC NAME> crosses the placenta, and may be excreted in breast milk. There is selective deposition of <GENERIC NAME> in newly formed keratin of hair, skin, and nails, which gradually moves to the surface of these appendages.

Metabolism:

<GENERIC NAME> undergoes metabolism to inactive metabolites, principally 6- desmethylgriseofulvin, or its glucuronide conjugate.

Excretion:

The terminal plasma half life ranges from 9.5-21 hours, with considerable intersubject variability. The majority of the dose, as 6-desmethylgriseofulvin or the glucuronide conjugate, and other metabolites is excreted in the urine, with less than 1% administered dose beinge excreted as unchanged <GENERIC NAME>. The remainder of the dose, principally as metabolites, is excreted in bile and faeces.

Renal insufficiency does not lead to accumulation.

* 1. **Preclinical safety data**

<GENERIC NAME> can induce aneuploidy and meiotic delay in mouse oocytes following oral administration of high doses, i.e. 250mg/kg or greater. In addition, <GENERIC NAME> caused increases in numerical and structural chromosome aberrations in mouse spermatocytes at doses of 500mg/kg and above. Aneuploidy was observed at doses of 1500mg/kg.

<GENERIC NAME> administered to rats and mice during pregnancy has been associated with foetotoxicity and foetal malformations. Long-term administration of high doses of <GENERIC NAME> with food has been reported to induce hepatomas in mice and thyroid tumours in rats but not hamsters (see contraindications). The effects in mice may be due to a species specific effect on porphyrin metabolism.

# PHARMACEUTICAL PARTICULARS

# List of excipients

# <REGARDING THE APPROVAL>

# Incompatibilities

# <REGARDING THE APPROVAL>

# Shelf life

# <REGARDING THE APPROVAL>

* 1. **Special precautions for storage**

<REGARDING THE APPROVAL>

* 1. **Nature and contents of container**

<REGARDING THE APPROVAL>

* 1. **Special precautions for disposal**

<REGARDING THE APPROVAL>

1. **MARKETING AUTHORISATION HOLDER**

<REGARDING THE APPROVAL>

1. **MARKETING AUTHORISATION NUMBER(S)**

<REGARDING THE APPROVAL>

1. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<REGARDING THE APPROVAL>

1. **DATE OF REVISION OF THE TEXT [[1]](#footnote-1)**

<REGARDING THE APPROVAL>

1. Ref: Griseofulvin, MHRA, 30/11/2011 [↑](#footnote-ref-1)