Public Assessment Report

Decentralised Procedure

Griseofulvin 500mg Tablets

UK/H/1773/001/DC

UK licence no: PL 20117/0109

Morningside Healthcare Limited
LAY SUMMARY

On the 9th May 2010, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Limited a Marketing Authorisation (licence) for the medicinal product Griseofulvin 500mg Tablets (PL 20117/0109). This licence was granted via the decentralised procedure (UK/H/1773/001/DC), with the UK as the Reference Member State (RMS) and Ireland as a Concerned Member State (CMS).

Griseofulvin is an anti-fungal agent. Griseofulvin 500mg Tablets is used to treat fungal infections of the hair, skin, scalp, groin feet and nails. It does this by incorporating into the skin, hair and nails.

This application is based on a reference product with a valid UK licence. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Griseofulvin 500mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
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# Module 1

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<th>Product Name</th>
<th>Griseofulvin 500mg Tablets</th>
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<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Griseofulvin</td>
</tr>
<tr>
<td>Form</td>
<td>Film-Coated Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>500mg</td>
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</table>
| MA Holder          | Morningside Healthcare Limited  
|                    | 115 Narborough Road, Leicester, UK |
| RMS                | UK                         |
| CMS                | Ireland                    |
| Procedure Number   | UK/H/1773/01/DC            |
| End of Procedure   | 9th May 2010               |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Griseofulvin 500mg Tablets (PL 20117/0109) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Griseofulvin 500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 500mg griseofulvin
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White to off white, round, biconvex film-coated tablet.

4 CLINICAL PARTICULARS
4.1 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 griseofulvin 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 griseofulvin is not justified in the treatment of minor or trivial infections that will respond to topical therapy.

Before prescribing Griseofulvin Tablets, consideration should be given to national and/or local guidance on the appropriate use of antifungals.

4.2 Posology and method of administration
General:
For oral administration.
Tablets should be swallowed whole with a glass of water. Griseofulvin 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. Griseofulvin 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
Griseofulvin 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 griseofulvin 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 therapy 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.

4.3 Contraindications
Griseofulvin is contraindicated in patients who have:
- Hypersensitivity to griseofulvin 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

4.4 Special warnings and precautions for use
Griseofulvin is recommended after a high fat meal for increased absorption and minimising GI distress.

Griseofulvin is contraindicated in patients with severe hepatic impairment, see section 4.3. In patients with minor to moderate hepatic impairment, griseofulvin 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.

Griseofulvin is contraindicated in patients with Systemic Lupus Erythematosus (SLE), see section 4.3; griseofulvin 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 griseofulvin induces tumours in some species, but not others. The clinical relevance of this to man is unknown, but griseofulvin should not be used prophylactically.

Griseofulvin 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.

Griseofulvin 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 griseofulvin to such patients. It should be noted that such patients have been satisfactorily treated with griseofulvin without sequelae.

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

Consumption of alcohol in association with griseofulvin 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 griseofulvin therapy.

In patients undergoing long term griseofulvin 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 griseofulvin may cause blood disorders, see section 4.8.
In common with any antibiotic, therapy with griseofulvin may result in the overgrowth of non-susceptible organisms, i.e. bacteria or yeasts, or non-dermatophyte fungi, that are often cofactors in tinea infections, especially tinea pedis. Additional therapy is required to control or eradicate such organisms, as griseofulvin is ineffective.

Griseofulvin is not effective in infections due to Candida albicans, Aspergillus sp., Malassezia furfur (Pityriasis versicolor) and Nocardia sp. It has no antibacterial effects.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal Products:
Griseofulvin may depress plasma levels, and therefore the efficacy, of concomitantly administered medicinal products that are metabolised by cytochrome P450 3A4.

Interactions of Griseofulvin with other drugs:
Ciclosporin: concomitant administration may result in a reduction of ciclosporin plasma levels, necessitating a dosage adjustment. Plasma levels of ciclosporin should be monitored during griseofulvin 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 griseofulvin therapy, and for 8 days post therapy cessation.

Methadone: depression of methadone plasma levels may occur during griseofulvin 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 griseofulvin 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 griseofulvin 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 griseofulvin:
Concurrent administration of other medicinal products that induce metabolising enzymes may result in a reduction of griseofulvin 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 griseofulvin 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 griseofulvin enhances the central nervous system effects of alcohol. There are also reports that griseofulvin and alcohol use result in an “Antabuse” type reaction. Patients should be cautioned to avoid alcohol and all alcohol containing products while undergoing griseofulvin therapy. See also section 4.8.

4.6 Pregnancy and lactation

Pregnancy:
There are case reports of human foetal abnormalities associated with griseofulvin. There are no adequate and well controlled studies in man, and inadequate epidemiological data. Griseofulvin has been shown to be teratogenic and embryotoxic in mice and rats. (see section 5.3). Griseofulvin is suspected to cause serious birth defects when administered during pregnancy. Griseofulvin 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
**Griseofulvin 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 griseofulvin therapy, and for 6 months post therapy cessation.**

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

**4.7 Effects on ability to drive and use machines**
Griseofulvin 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.

**4.8 Undesirable effects**
The following frequencies are used for the description of the occurrence of undesirable effects:

<table>
<thead>
<tr>
<th>Frequency Grouping</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Very common</td>
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<tr>
<td>Common</td>
<td>$\geq 1/100$, $&lt; 1/10$</td>
</tr>
<tr>
<td>Uncommon</td>
<td>$\geq 1/1,000$, $&lt; 1/100$</td>
</tr>
<tr>
<td>Rare</td>
<td>$\geq 1/10,000$, $&lt; 1/1,000$</td>
</tr>
<tr>
<td>Very rare</td>
<td>$&lt; 1/10,000$</td>
</tr>
</tbody>
</table>

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, erythema multiforme, photosensitivity on exposure to intense natural or artificial sunlight.
Rare: precipitation of Systemic Lupus Erythematosus, 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 cholestasis, hepatitis.

**4.9 Overdose**
No case of overdose has been reported.

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

**Treatment:**
There is no specific antidote to griseofulvin. 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 haemopoietic, hepatic and nephritic parameters and electrolytes is recommended.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antifungals for systemic use
ATC code: D01BA01
Griseofulvin 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 interfering 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, griseofulvin 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-griseofulvin complex.

Griseofulvin then enters the dermatophyte through energy dependent transport processes and binds to the fungal microtubules, interfering with, and inhibiting mitosis, and the deposition of fungal cell walls.

Mycology:
Griseofulvin has antifungal activity against the following dermatophytes, although there is species and strain variability in susceptibility.


Microsporum audouinii, M. Canis, M. gypseum.

Epidermophyton floccosum.

Griseofulvin has no activity against dermatophyte fungi of other genera, non-dermatophyte 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.

5.2 Pharmacokinetic properties
Absorption:
The absorption of griseofulvin from the gastrointestinal tract is variable 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.
Griseofulvin exhibits linear pharmacokinetics.

Distribution:
The volume of distribution is about 0.7 L / Kg, and griseofulvin is ca 80 % bound to plasma proteins, predominantly serum albumin.
Griseofulvin crosses the placenta, and may be excreted in breast milk. There is selective deposition of griseofulvin in newly formed keratin of hair, skin, and nails, which gradually moves to the surface of these appendages.

Metabolism:
Griseofulvin undergoes metabolism to inactive metabolites, principally 6- desmethyglyriseofulvin, 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-desmethyglyriseofulvin or the glucuronide conjugate, and other metabolites is excreted in the urine, with less than 1% administered dose being excreted as unchanged griseofulvin. The remainder of the dose, principally as metabolites, is excreted in bile and faeces.
Renal insufficiency does not lead to accumulation.
5.3 Preclinical safety data
Griseofulvin can induce aneuploidy and meiotic delay in mouse oocytes following oral administration of high doses, i.e. 250mg/kg or greater. In addition, griseofulvin 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. Griseofulvin administered to rats and mice during pregnancy has been associated with foetotoxicity and foetal malformations. Long-term administration of high doses of griseofulvin 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Tablet core: Maize starch
Microcrystalline cellulose E 460
Sodium laurilsulphate
Povidone E 1201
Magnesium stearate E 470b
Film coat: Hypromellose E 464
Ethylcellulose E 462
Polysorbate 80 E 433
Propylene glycol E 1520

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Unopened container : 24 Months
Opened container : 6 Months

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Polypropylene (PP) tablet container, with aluminium induction seal and linear low density polyethylene (LLDPE) screw closure. Tablet containers with 90 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Morningside Healthcare Ltd
115 Narborough Road, Leicester, LE3 0PA
UK

8 MARKETING AUTHORISATION NUMBER(S)
[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25/05/2010

10 DATE OF REVISION OF THE TEXT
25/05/2010
Module 3
Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Griseofulvin 500mg Tablets

Griseofulvin

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. WHAT GRISEOFULVIN IS AND WHAT IT IS USED FOR
2. BEFORE YOU TAKE GRISEOFULVIN
3. POSSIBLE SIDE EFFECTS
4. HOW TO TAKE GRISEOFULVIN
5. HOW TO STORE GRISEOFULVIN
6. FURTHER INFORMATION

1. WHAT GRISEOFULVIN IS AND WHAT IT IS USED FOR

Griseofulvin 500mg Tablets contain an anti-fungal agent called Griseofulvin. Griseofulvin kills the fungi that cause infections of the skin, scalp, groin ("jock itch"), feet ("athlete's foot"), and nails. It does this by being incorporated into the skin, hair and nails, which takes the same time as they take to grow. This is why treatment lasts for a long time.

2. BEFORE YOU TAKE GRISEOFULVIN

Do not take Griseofulvin:
- If you are allergic (hypersensitive) to griseofulvin or any of the other ingredients of the tablet (see section 2)
- If you suffer from a rare allergy called porphyria
- If you suffer from a rare painful skin and tissue disease called Systemic Lupus Erythematosus, or SLE
- If you have severe liver disease
- If you are pregnant, or you think you might be pregnant, or you are planning to get pregnant
- If you are breastfeeding

If any of the above apply to you, do not take the tablets and go back to your doctor.

Takespecial care with Griseofulvin
If any of the following points apply to you, you should discuss them with your doctor before starting to take Griseofulvin:
- If you have liver disease, your doctor may need to check on you while taking this medicine
- If you have had an allergic (hypersensitivity) reaction previously to pencillin or to cephalosporins, both types of antibiotic. There is a possibility you may be sensitive to griseofulvin
- If you are ruining on oral contraception, the "pill", griseofulvin may prevent it working. All sexually active patients should use additional barrier contraception, such as condoms, throughout griseofulvin therapy, and for four weeks (female) and 6 months (male) after stopping the therapy
- If you are a man planning to father a child, griseofulvin may damage your sperm. You should not father a child while taking griseofulvin and for six months after you have stopped taking it. You and your partner should use additional contraceptive measures to prevent pregnancy during this period
- If you suffer from a rare painful skin and tissue disease called Systemic Lupus Erythematosus, or SLE
- If you have had an allergic (hypersensitivity) reaction previously to pencillin or to cephalosporins, both types of antibiotic. There is a possibility you may be sensitive to griseofulvin
- If you are ruining on oral contraception, the "pill", griseofulvin may prevent it working. All sexually active patients should use additional barrier contraception, such as condoms, throughout griseofulvin therapy, and for four weeks (female) and 6 months (male) after stopping the therapy
- If you are a man planning to father a child, griseofulvin may damage your sperm. You should not father a child while taking griseofulvin and for six months after you have stopped taking it. You and your partner should use additional contraceptive measures to prevent pregnancy during this period
- If you suffer from a rare painful skin and tissue disease called Systemic Lupus Erythematosus, or SLE
- Alcoholic drinks, and anything containing alcohol, should be avoided while you are taking Griseofulvin. Griseofulvin may make the alcohol affect you more. Alcohol and griseofulvin may cause a disulfatreaction-you will feel sick, may be sick, bluish, and have an irregular heartbeat, and chest and/or abdominal pain.
- Your skin becomes more sensitive to sunlight or ultraviolet (UV) light when taking Griseofulvin. Avoid exposure to strong sunlight, or artificial UV light such as sunbeds.
- Griseofulvin may result in the overgrowth of un-susceptible organisms, i.e. bacteria or yeasts, or non-dermatophyte fungi that are often co-factors in tinea infections, especially tinea pedis. Additional therapy is required to control or eradicate such organisms, as griseofulvin is ineffective.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important to tell your doctor if you are taking any of the following:
- Ciclosporin, a medicine used after organ transplantation, it may not work as well
- Any medicines to thin your blood, such as warfarin, your dose may need to be increased, and the doctor will want to check on you during treatment, and for 5 days after finishing treatment with griseofulvin
- Methadone, used to treat addiction, or as a pain killer, the dose may need to be increased to maintain the same effect
- Oral contraceptives may not work as well, and as you should not become pregnant during treatment with griseofulvin, you should use additional contraceptive measures, such as a condom
- Barbiturates, such as phenobarbitonal, used to treat convulsions or as a sedative, it may prevent griseofulvin from being effective
- Non-steroidal anti-inflammatory agents, used to relieve pain or inflammation, it may prevent griseofulvin from being effective
- Primidone, used to treat convulsions
- Droxycycline, a antibiotic and a vitamin D supplement
- Medicines for sedation, or relief of anxiety, they may prevent griseofulvin from being effective

Taking Griseofulvin with food and drink
For the best effects, Griseofulvin should be taken after a high fat meal. This helps to increase the absorption of griseofulvin into your body, so it can be effective against the infection and also reduce stomach discomfort.

Alcoholic drinks, and anything containing alcohol, should be avoided while you are taking Griseofulvin. Griseofulvin may make the alcohol affect you more. Alcohol and griseofulvin may cause a disulfatreaction-you will feel sick, may be sick, bluish, and have an irregular heartbeat, and chest and/or abdominal pain.

Pregnancy and breastfeeding
Ask your doctor or pharmacist before taking any medicine.
- If you are pregnant, or think you might be pregnant-do not take Griseofulvin-see your doctor. It may harm your baby.
- If you are taking griseofulvin and you get pregnant-see your doctor immediately.
- Griseofulvin stops oral contraceptives working as effectively, so you should use additional contraception, such as a condom, while taking griseofulvin and for 4 weeks afterwards.
- If you are breastfeeding-do not take Griseofulvin-see your doctor.


**3. HOW TO TAKE GRISEOFULVIN**

Always take Griseofulvin exactly as your doctor has told you. You should not take more or less of the medicine than your doctor prescribes. The usual adult dose is 500 mg to 1000 mg a day, given as either a single dose, or in two equal doses.

For children, the dose depends on the age and the weight of the child, and is usually 10 mg / kilogram of body weight per day. The dose is usually given as two equal doses. Make sure you follow the instructions of the doctor.

The length of time you have to take your medicine will be decided by your doctor. For fungal infections of the scalp or body, this could be 4-6 weeks, for infections of the scalp or face it could be 4-8 weeks, and for infections of the nails, 8-12 months.

**If you take more Griseofulvin than you should**

You should contact your doctor, or the nearest hospital at once, and follow their advice. Remember to tell them how many extra tablets have been taken, and if you are taking any other medicines.

**If you forget to take Griseofulvin**

If you forget to take a tablet, take it when you remember, and if it is more than 12 hours after your next tablet, do not take a double dose to make up for the forgotten tablet.

**If you stop taking Griseofulvin**

Do not stop taking Griseofulvin unless your doctor tells you to. You must keep taking it, even if you feel better, and the skin or nails seem to be cured. You should keep taking it for at least 2 weeks after all signs of infection have gone. If you stop early, the infection may come back.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Griseofulvin can cause side effects, although not everybody gets them.

The most common side effects are headache and stomach discomfort at the start of treatment, but these usually disappear on continuing treatment.

**If you get any of the following rare, or very rare side effects, see your doctor immediately**

- Rare, affecting more than 1 in 10,000 patients, but less than 1 in 1,000 patients:
  - Low numbers of certain types of blood cells, characterised by increased minor infections, sore throat, feeling tired and weak
  - Sore, painful, swollen skin, and joints, butterfly rash (attack of Systemic Lupus Erythematosus) severe skin reactions, including severe reddening of the skin, raised, itchy, painful skin rash

**Very rare, affecting fewer than 1 in 10,000 patients**

- Changes to your liver, with signs such as lower back pain, very pale urine, yellowing of the skin and/or the whites of the eyes

Common, affecting more than 1 in 100 patients, but less than 1 in 10 patients

- Headache
- Diarrhoea, being a kick, feeling sick, stomach discomfort

**Uncommon, affecting more than 1 in 1000 patients, but less than 1 in 100 patients**

- Lack of co-ordination, confusion, dizziness, drowsiness, slurred speech, irritability, tingling and numbness in fingers and toes
- Anorexia, changes in taste sensation
- Blistering and peeling of the skin, lumpy skin, with or without a weeping liquid, reddening and burning of the skin you should contact your doctor immediately

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5. HOW TO STORE GRISEOFULVIN**

Keep out of reach of children.

Do not use Griseofulvin after the expiry date which is stated on the label after Exp. The expiry date refers to the last day of that month.

To be used within 6 months after first opening the container.

Do not store above 25°C.

After opening the container, screw the cap back tightly after every use.

Medicines should not be disposed off via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**3. FURTHER INFORMATION**

**What Griseofulvin contains**

- The active substance is Griseofulvin 500 mg in each tablet.
- The other ingredients are: microcrystalline cellulose, sodium lauryl sulphate, povidone, magnesium stearate, hypromellose, ethylcellulose, polyvinyl alcohol, and propylene glycol.

**What Griseofulvin looks like and contents of the pack**

Griseofulvin 500mg Tablets are white to off white, round, biconvex film-coated tablets.

They are packed in a plastic tablet container with a plastic screw cap.

Containers of 90 tablets are available.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

Morningside Healthcare Ltd.
115 Narborough Road
Leicester, LE3 6PA, UK.

**Manufacturer**

Morningside Pharmaceuticals Ltd.
5 Pavilion Way, Loughborough
LE11 5GW, UK.

**Name of the product in different member states of the EEA:**

**United Kingdom**

Griseofulvin 500mg Tablets

**Ireland**

Griseofulvin Moringa 500 mg Film-coated Tablets

Name and address of the local representative:

[To be completed nationally]

This leaflet was last updated in March 2010.
Module 4
Labelling

Carton

Label
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

On 9th May 2010, Ireland and the UK agreed to grant a Marketing Authorisation to Morningside Healthcare Limited for the medicinal product Griseofulvin 500mg Film Coated Tablets. The licence was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/1773/01/DC). After the national phase, licences were granted in the UK on 25th May 2010 (PL 20117/0109).

This application was made under Article 10.1 of Directive 2001/83/EC for Griseofulvin 500mg Film Coated Tablets, containing the known active substance griseofulvin. The reference medicinal product for this application is Grisovin 500mg tablets, first licensed in the UK to Glaxo Operation UK Limited on 13/1/1988 (PL 00004/5061). The licence subsequently underwent a change of ownership and is now Griseofulvin 500mg Tablets (PL 17736/0083) licensed to Chemidex Pharma Limited.

The active ingredient, griseofulvin is a fungistatic antibiotic that inhibits fungal cell division by disruption of the mitotic spindle structure. On entering the systemic circulation, griseofulvin 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-griseofulvin complex. Griseofulvin then enters the dermatophyte through energy dependent transport processes and binds to the fungal microtubules, interfering with, and inhibiting mitosis, and arresting cell division. It may also interfere with DNA production. It is active against the common dermatophytes, including some species of *Epidermophyton*, *Microsporum*, or *Trichophyton*.

Griseofulvin is used orally in the treatment of dermatophyte infections. It is generally given when such infections involve the scalp, hair, nails, and skin and do not respond to topical treatment; infections of the soles of the feet, the palms of the hands, and the nails. The usual dose is 0.5 to 1 g daily in single or divided doses; children have been given 10 mg/kg daily. These doses are for preparations of griseofulvin of reduced particle size, sometimes known as microcrystalline or microsize griseofulvin. Doses have been reduced by about one-quarter when preparations, available in some countries, containing ultramicrocrystalline or ultramicrosize griseofulvin are used. Griseofulvin should be given with or after meals. The duration of treatment depends on the thickness of the keratin layer: 2 to 8 weeks for infections of the hair and skin, up to 6 months for infections of the fingernails, and 12 months or more for infections of the toenails.

No new preclinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application was for a generic version of product that has been licensed for over 10 years.

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Griseofulvin 500mg Film Coated Tablets, to that of the reference product, Griseofulvin 500mg tablets (Chemidex Pharma Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP)
are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.
## ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Griseofulvin 500 mg Film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Griseofulvin</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Anti-fungal agent D01BA01</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated tablet 500 mg</td>
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<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1773/01/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20117/0109</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Morningside Healthcare Limited</td>
</tr>
<tr>
<td></td>
<td>115 Narborough Road</td>
</tr>
<tr>
<td></td>
<td>Leicester, LE3 0PA, UK</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1  QUALITY ASPECTS

DRUG SUBSTANCE

INN  Griseofulvin

- Chemical name: \((1'S,3-6'R)-7\text{-chloro-2',4,6\text{-trimethoxy-6'}\text{methylspiro[benzofuran-2(3H),1'}-2\text{]cyclohexene}]3,4'\text{-dione}}\)

Structure

![Chemical Structure](image)

Molecular formula: \(\text{C}_{17}\text{H}_{17}\text{ClO}_{6}\)

Molecular weight: 352.8

General Properties

Description: Griseofulvin is a white or yellowish white, microfine powder, practically insoluble in water, freely soluble in dimethylformamide and tetrachloroethane, slightly soluble in anhydrous ethanol and methanol.

Manufacture

All aspects of the manufacture and control of the active substance griseofulvin are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT

Other ingredients

The drug product is a film-coated tablet containing 500mg of the active substance, griseofulvin. The tablets are white to off white, round, bioconvex in shape and plain on both sides.

Other ingredients consist of pharmaceutical excipients, namely maize starch, microcrystalline cellulose (E460), sodium laurilsulphate, povidone E1201 and magnesium stearate (E470b) making up the tablet core; and hypromellose E464, ethylcellulose E462, polysorbate 80 E433 and propylene glycol E1520 making up the film coating. Appropriate justification for the inclusion of each excipient has been provided.

All ingredients within the tablet comply with their relevant Ph Eur monographs. Satisfactory Certificates of Analysis have been provided for each excipient. The magnesium stearate has been confirmed as being of vegetable origin. None of the excipients used contains material of animal or human origin.

Pharmaceutical Development

Suitable pharmaceutical development data have been provided for this application.
The physico-chemical properties of the drug product have been compared with the originator product. These data demonstrate that the proposed product can be considered a generic medicinal product of Griseofulvin 500mg Tablets licensed to Chemidex Pharma Limited.

**Dissolution and Impurity profiles**
Comparative dissolution and impurity data were provided for the test and reference products. The dissolution and impurity profiles were found to be similar, with all impurities within the specification limits.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. Satisfactory analytical results from batches representative of commercial scale were provided.

**Finished product specification**
The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided for three pilot scale batches of the product, which demonstrate that the batches are compliant with the proposed specifications. Confirmation is provided that validation will be performed on the first three commercial scale batches. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**
The finished product is licensed for marketing in PP (polypropylene) tablet containers with an LDPE (low density polyethylene) screw closure, with an aluminium induction seal. The containers hold 90 tablets.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months, when the container is unopened and 6 months after the container has been opened has been set, which is satisfactory. Storage instructions are ‘Do not store above 25°C.’.

**Bioequivalence Study**
A bioequivalence study was submitted comparing the test product, Griseofulvin 500 mg tablets, to the reference product Griseofulvin 500 mg Tablets (Chemidex Pharma Limited).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.
Quality Overall Summary
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA form
The MAA form is pharmaceutically satisfactory.

Conclusion
The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. On this basis, and considering the bioequivalence data provided, the applicant’s claim that Griseofulvin 500 mg Tablets is a generic medicinal product of Griseofulvin 500 mg Tablets (Chemidex Pharma Limited) appears justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation was therefore granted.

III.2 PRE-CLINICAL ASPECTS
Critical evaluation of the Non-Clinical Overview and Summary
The pharmacodynamic, pharmacokinetic and toxicological properties of griseofulvin are well known. Therefore, no further studies are required and the applicant provides none. An overview based on a literature review is, thus, appropriate.

The non-clinical overview was written by a suitably qualified person. The report refers to nine references up to 2008.

The lack of an environmental risk assessment is justified since the product is a generic version of an already approved one and it is not likely to change the total market of griseofulvin.

The preclinical information conveyed in sections 4.6 and 5.3 of the SPC are based on the innovator’s and reference product’s SPC. This is acceptable.

Conclusions
There are no objections to approval of Griseofulvin 500mg Film-coated Tablets from a non-clinical point of view.
III.3 CLINICAL ASPECTS

3.1 Introduction

3.2 Clinical Study Reports
The applicant presents a very brief overview of clinical studies of safety and efficacy with Griseofulvin and this is acceptable for this type of application. The applicant has conducted a bioequivalence study for Griseofulvin 500 mg tablets, details of which are given below.

3.2.1 Pharmacokinetic Studies
An open label, randomized, two treatment, two sequence, two period, crossover, single-dose comparative oral bioavailability study of Griseofulvin 500 mg tablets (Test), and Griseofulvin 500 mg tablets (Reference), in 14 healthy, adult, male, human subjects under fed conditions.

Population(s) studied
14 healthy adult male human subjects were enrolled as per the protocol.

Dose(s) administered (test/reference)
A single oral dose (500mg) of the assigned formulation in the fed state.

Duration of sampling following dosing
Serial blood samples were drawn pre dose and up to 120 hours post dose.

Sampling frequency around $T_{\text{max}}$
$T_{\text{max}}$ for Griseofulvin is around 2-4 hrs and sampling frequency was sufficient for accurate $C_{\text{max}}$ estimation.

Washout period
There was a washout period of 10 days between the two periods of the study and this was sufficient to avoid carryover as evidenced by undetectable levels in the pre-dose samples in period 2.

Pre-defined bioequivalence acceptance criteria
Bioequivalence was to be concluded if the 90% Confidence Intervals for the ratios of the means of ln-transformed pharmacokinetic parameters $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ of Griseofulvin for the test and reference formulations were within the bioequivalence limits of 80%-125%.

Analytical methods
Plasma griseofulvin concentrations were measured using a validated LC-MS-MS method.

Method of data analysis
Pharmacokinetic parameters ($T_{\text{max}}$, $C_{\text{max}}$, $AUC_{0-t}$, $AUC_{0-\infty}$, kel and $t_{1/2}$) were calculated from the plasma griseofulvin concentrations (drug concentration time profiles) by non-compartmental analysis. The 90% Confidence Intervals for the ratios of the means of ln-transformed pharmacokinetic parameters $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ were also calculated.

Results
Bioequivalence results for Ln-transformed test/reference ratios with 90% Confidence Intervals:
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test</th>
<th>Reference</th>
<th>T/R ratio</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>1857.11</td>
<td>1870.68</td>
<td>99.27</td>
<td>91.25-108.01</td>
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<tr>
<td>AUC_{t} (ng.h/mL)</td>
<td>39597.69</td>
<td>42991.61</td>
<td>92.11</td>
<td>82.12-103.30</td>
</tr>
<tr>
<td>AUC_{\infty} (ng.h/mL)</td>
<td>41555.83</td>
<td>43895.72</td>
<td>94.67</td>
<td>84.66-105.86</td>
</tr>
</tbody>
</table>

**ASSESSOR’S COMMENT**

The two-period, two-sequence cross-over study design is appropriate. Study drug was administered after a supervised meal. It is known that the bioavailability of Griseofulvin is improved when administered with food. The bioequivalence study under fed conditions is therefore acceptable.

None of the pre-dose samples contained detectable level of Griseofulvin, length of the washout period was adequate. Blood collection time up to 120h post-dose was sufficient.

Analytical methods are satisfactory. The methods of statistical analysis used are appropriate. The 90% confidence intervals for the ln-transformed AUC and C_{max} for Griseofulvin lie within the acceptance criteria of 80-125%.

Based on the submitted bioequivalence study, the test and reference products, after a single dose (500 mg) administration, are considered to be bioequivalent.

### 3.2.2 Pharmacodynamics

The applicant presents clinical and non-clinical overviews that include a description of the pharmacodynamics of Griseofulvin. The pharmacodynamic characteristics of Griseofulvin have been well studied in the past. There would be no particular concerns for a generic formulation.

### 3.3 Post-marketing experience

The applicant’s medicinal product has not been marketed in any country. Griseofulvin as an active ingredient has a well-established and an acceptable level of safety in the indications approved for the reference product, which was first authorised in UK.

### 3.4 Clinical Expert

The clinical overview was written in 2007 by a suitably qualified person. There are 12 references up to 2007. Although the overview adequately covers the BE study conducted by the applicant, it provides inadequate literature to support the use of this medicinal product in the indications applied for in the SPC.

### 3.4 Pharmacovigilance system

A satisfactory pharmacovigilance report has been provided.

### 3.5 Benefit-Risk assessment

The benefit-risk assessment is favourable.
The applicant’s Griseofulvin tablets are similar to the reference product. Apart from those mentioned in the SPC no specific risks are related to Griseofulvin as an active ingredient. A risk management plan is therefore not required.

**Risk Management Plan**
Not required.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labelling are medically acceptable.

**MAA form**
The MAA forms are medically satisfactory.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Griseofulvin 500mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
The applicant’s Griseofulvin 500mg Tablets has been demonstrated to be a generic version of the reference product Griseofulvin 500mg Tablets (Chemidex Pharma Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPCs, PIL and labelling texts are satisfactory and consistent with those for the reference product.

A user consultation with target patient groups on the package information leaflet (PIL) text has been performed. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Griseofulvin 500mg Tablets and the reference product Griseofulvin 500mg Tablets (Chemidex Pharma Limited), are interchangeable. Extensive clinical experience with griseofulvin is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.
# Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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