Public Assessment Report

Decentralised Procedure

Itraconazole 100mg Capsules

UK/H/1317/01/DC
UK licence no: PL 20796/0007

Pharmakal Limited
LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Pharmakal Limited a Marketing Authorisation (licence) for the medicinal product Itraconazole 100mg Capsules. This medicine is available on prescription only.

Itraconazole Capsules belong to a group of medicines called antimycotics for systemic use, also known as “antifungals”, which are used to treat infections caused by fungi including yeasts. Itraconazole Capsules are used to treat fungal infections of the vagina, skin, lungs, mouth, nail and internal organs.

The test product was considered the same as the original product Sporanox 100mg Capsules (Janseen-Cilag S.A) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Itraconazole 100mg Capsules outweigh the risks; hence a Marketing Authorisation has been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure  
Module 2: Summary of Product Characteristics  
Module 3: Product Information Leaflet  
Module 4: Labelling  
Module 5: Scientific Discussion  
1 Introduction  
2 Quality aspects  
3 Pre-clinical aspects  
4 Clinical aspects  
5 Overall conclusions  
Module 6 Steps taken after initial procedure
Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Itraconazole 100mg Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Itraconazole</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Capsule, hard</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>100mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Pharmakal Limited</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Portugal and Netherlands</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1317/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 - 12/02/2009</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
ITRACONAZOLE 100mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 100mg itraconazole.
Excipients: Sucrose 224.31mg per capsule.
For a full list excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsules, hard
Hard gelatin capsules (size 0) with a green opaque cap and body containing yellowish-beige spherical microgranules

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
1. Vulvovaginal candidosis.
2. Pityriasis versicolor.
3. Dermatophytoises caused by organisms susceptible to itraconazole (Trichophyton spp., Microsporum spp., Epidermophyton floccosum) e.g. tinea pedis, tinea cruris, tinea corporis, tinea manuum.
4. Oropharyngeal candidosis.
5. Onychomycosis caused by dermatophytes and/or yeasts.
6. The treatment of histoplasmosis.
7. Itraconazole is indicated in the following systemic fungal conditions when first-line systemic anti-fungal therapy is inappropriate or has proved ineffective. This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity.
   - Treatment of aspergillosis, candidosis
   - Treatment of cryptococcosis (including cryptococcal meningitis) : in immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system.
   - Maintenance therapy in AIDS patients to prevent relapse of underlying fungal infection. Itraconazole is also indicated in the prevention of fungal infection during prolonged neutropenia when standard therapy is considered inappropriate.

4.2 Posology and method of administration
Itraconazole is for oral administration and must be taken immediately after a meal for maximal absorption.
Treatment schedules in adults for each indication are as follows:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal candidosis</td>
<td>200mg twice daily for 1 day</td>
<td></td>
</tr>
<tr>
<td>Pityriasis versicolor</td>
<td>200mg once daily for 7 days</td>
<td></td>
</tr>
<tr>
<td>Tinea corporis, tinea cruris</td>
<td>100mg once daily for 15 days or 200mg once daily for 7 days</td>
<td></td>
</tr>
<tr>
<td>Tinea pedis, tinea manuum</td>
<td>100mg once daily for 30 days</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal candidosis</td>
<td>100mg once daily for 15 days</td>
<td>Increase dose to 200mg once daily for 15 days in AIDS or neutropenic patients because of</td>
</tr>
</tbody>
</table>
### Indication
### Dose
### Remarks

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onychomycosis (toenails with or without fingernail involvement)</td>
<td>200 mg once daily for 3 months</td>
<td>impaired absorption in these groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For skin, vulvovaginal and oropharyngeal infections, optimal clinical and mycological effects are reached 1-4 weeks after cessation of treatment and for nail infections, 6-9 months after the cessation of treatment. This is because elimination of itraconazole from skin, nails and mucous membranes is slower than from plasma.

The length of treatment for systemic fungal infections should be dictated by the mycological and clinical response to therapy:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis</td>
<td>200 mg once daily</td>
<td>Increase dose to 200 mg twice daily in case of invasive or disseminated disease</td>
</tr>
<tr>
<td>Candidosis</td>
<td>100-200 mg once daily</td>
<td>Increase dose to 200 mg twice daily in case of invasive or disseminated disease</td>
</tr>
<tr>
<td>Non-meningeal Cryptococcosis</td>
<td>200 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>200 mg twice daily</td>
<td>See 4.4. Special warnings and special precautions for use.</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>200 mg once daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg twice daily</td>
<td></td>
</tr>
<tr>
<td>Maintenance in AIDS</td>
<td>200 mg once daily</td>
<td>See note on impaired absorption below</td>
</tr>
<tr>
<td>Prophylaxis in neutropenia</td>
<td>200 mg once daily</td>
<td>See note on impaired absorption below</td>
</tr>
</tbody>
</table>

Impaired absorption in AIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. In such cases, blood level monitoring and if necessary, an increase in itraconazole dose to 200 mg twice daily, is indicated.

**Use in children**
Not recommended. See 4.4 Special warnings and special precautions for use.

**In Elderly:** Not recommended. See 4.4 Special warnings and special precautions for use.
Use in patients with renal impairment
The oral bioavailability of itraconazole may be lower in patients with renal insufficiency, a dose adjustment may be considered. See 4.4 Special warnings and special precautions for use.

Use in patients with hepatic impairment
Itraconazole is predominantly metabolised by the liver. The terminal half-life of itraconazole in cirrhotic patients is somewhat prolonged. The oral bioavailability in cirrhotic patients is somewhat decreased. A dose adjustment may be considered. See 4.4 Special warnings and special precautions for use.

4.3 Contraindications
Itraconazole is contra-indicated in patients who have shown hypersensitivity to the drug or its excipients.
Coadministration of the following drugs is contraindicated with Itraconazole capsules. (see also section 4.5 Interaction with other medicinal products and other forms of interaction):
- CYP3A4 metabolised substrates that can prolong the QT-interval e.g., astemizole, bepridil, cisapride, doxetilde, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole and terfenadine are contraindicated with Itraconazole capsules. Coadministration may result in increased plasma concentrations of these substrates which can lead to QTc prolongation and rare occurrences of torsades de pointes.
- CYP3A4 metabolised HMG-CoA reductase inhibitors such as lovastatin and simvastatin
- Triazolam and oral midazolam
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine)
- Eletriptan
- Nisoldipine
- Itraconazole capsules should not be administered for non-life threatening indications to patients receiving disopyramide or halofantrine.
Itraconazole capsules should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections. See 4.4 Special warnings and precautions for use.

4.4 Special warnings and precautions for use
Cardiac effects
• In a healthy volunteer study with Itraconazole IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed.
• Itraconazole has been shown to have a negative inotropic effect and Itraconazole has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.
  - Itraconazole should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dose and duration of treatment, and individual risk factors for congestive heart failure. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, Itraconazole should be discontinued.
  - Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be exercised when co-administering itraconazole and calcium channel blockers (see section 4.5, Interactions with other medicinal products and other forms of interaction) due to an increased risk of congestive heart failure.

Interaction Potential
• Itraconazole has a potential for clinically important drug interactions. (See 4.5: Interaction with other medicaments and other forms of interaction).
Reduced gastric acidity:
  - Absorption of itraconazole is impaired when gastric acidity is decreased. In patients also receiving acid neutralising medicines (e.g. aluminium hydroxide), these should be administered at least 2 hours after the intake of Itraconazole. In patients with achlorhydria, such as certain AIDS patients and patients on acid secretion suppressors (e.g. H2-antagonists, proton-pump inhibitors), it is advisable to administer Itraconazole with a cola beverage.
Use in children

- Clinical data on the use of Itraconazole capsules in paediatric patients is limited. Itraconazole capsules should not be used in paediatric patients unless the potential benefit outweighs the potential risks.

Use in elderly

- Clinical data on the use of Itraconazole capsules in elderly patients is limited. Itraconazole capsules should not be used in these patients unless the potential benefit outweighs the potential risks.

Hepatic effects

- Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Itraconazole. Some of these cases involved patients with no pre-existing liver disease. Some of these cases have been observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving Itraconazole treatment. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. In these patients treatment should be stopped immediately and liver function testing conducted. Most cases of serious hepatotoxicity involved patients who had pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking other hepatotoxic drugs. In patients with raised liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases liver enzyme monitoring is necessary.

Hepatic impairment

- Itraconazole is predominantly metabolised in the liver. A slight decrease in oral bioavailability in cirrhotic patients has been observed, although this was not of statistical significance. The terminal half-life was however significantly increased. The dose should be adapted if necessary.

Renal impairment

- The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. Dose adaptation may be considered.

Immunocompromised patients

- In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), the oral bioavailability of Itraconazole capsules may be decreased.

Patients with immediately life-threatening systemic fungal infections

- Due to the pharmacokinetic properties (See section 5.2), Itraconazole capsules are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

Patients with AIDS

- In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal or non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Neuropathy

- If neuropathy occurs which may be attributable to Itraconazole, treatment should be discontinued.

Cross-hypersensitivity

- There is no information regarding cross hypersensitivity between itraconazole and otherazole antifungal agents. Caution should be used in prescribing Itraconazole to patients with hypersensitivity to other azoles.

- In systemic candidosis, if fluconazole-resistant strains of Candida species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of Itraconazole therapy.

This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
4.5 Interaction with other medicinal products and other forms of interaction

1. Drugs affecting the absorption of itraconazole

Drugs that reduce the gastric acidity impair the absorption of itraconazole from Itraconazole capsules (See 4.4 Special warnings and special precautions for use).

2. Drugs affecting the metabolism of itraconazole:

Itraconazole is mainly metabolised through the cytochrome CYP3A4. Interaction studies have been performed with rifampicin, rifabutin and phenytoin, which are potent inducers of CYP3A4. Since the bioavailability of itraconazole and hydroxy-itraconazole was decreased in these studies to such an extent that efficacy may be largely reduced, the combination of itraconazole with these potent enzyme inducers is not recommended. No formal study data are available for other enzyme inducers, such as carbamazepine, phenobarbital and isoniazid, but similar effects should be anticipated. Potent inhibitors of this enzyme such as ritonavir, indinavir, clarithromycin and erythromycin may increase the bioavailability of itraconazole.

3. Effects of itraconazole on the metabolism of other drugs:

3.1 Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family. This can result in an increase and/or a prolongation of their effects, including side effects. After stopping treatment, itraconazole plasma levels decline gradually, depending on the dose and duration of treatment (see 5.2 Pharmacokinetic Properties). This should be taken into account when the inhibitory effect of itraconazole on co-administered drugs is considered.

Examples are:

- The following drugs are contraindicated with itraconazole:
  - Astemizole, bepridil, cisapride, doxetilide, levacetylmethadol (levomethadyl), mizolastine, pimozide, quinidine, sertindole or terfenadine are contraindicated with Itraconazole since co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsades de pointes.
  - CYP3A4 metabolised HMG-CoA reductase inhibitors such as lovastatin and simvastatin.
  - Triazolam and oral midazolam.
  - Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).
  - Eletriptan
  - Nisoldipine

Caution should be exercised when co-administering itraconazole with calcium channel blockers. In addition to possible pharmacokinetic interactions involving the drug metabolising enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole.

- The following drugs should be used with caution and their plasma concentrations effects or side effects should be monitored. Their dosage, when co-administered with itraconazole, should be reduced if necessary:
  - Oral anticoagulants
  - HIV protease inhibitors such as ritonavir, indinavir, saquinavir
  - Certain antineoplastic agents such as vinca alkaloids, busulfan, docetaxel and trimetrexate
  - CYP3A4 metabolised calcium channel blockers such as dihydropyridines and verapamil
  - Certain immunosuppressive agents: ciclosporin, tacrolimus, rapamycin (also known as sirolimus)
  - Certain CYP3A4 metabolised HMG-CoA reductase inhibitors such as atorvastatin
  - Certain glucocorticoids such as budesonide, dexamethasone, fluticasone and methylprednisolone
  - Digoxin
  - Others: carbamazepine, ciltazol, buspirone, disopyramide, alfentanil, alprazolam, brotizolam, midazolam IV, rifabutin, ebastine, fentanyl, halofantrine, repaglinide and reboxetine. The importance of the concentration increase and the clinical relevance of these changes during co-administration with itraconazole remain to be established.

3.2 No interaction of itraconazole with AZT (zidovudine) and fluvastatin has been observed. No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.
4. Effect on protein binding:
In vitro studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide or sulphadimidine.

4.6 Pregnancy and lactation
Pregnancy
There are no data from the use of itraconazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Itraconazole capsules must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus. Itraconazole is not recommended in women of childbearing potential not using contraception.
Lactation
A very small amount of itraconazole is excreted in human milk. Itraconazole capsules must not be used during lactation.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects
Approximately 9% of patients can be expected to experience adverse reactions while taking itraconazole. In patients receiving prolonged (approximately 1 month) continuous treatment, the incidence of adverse events was higher (about 15%). The most frequently reported adverse experiences were of gastrointestinal, hepatic and dermatological origin. Within each system organ class, the adverse reactions are ranked under the headings of frequency, using the following convention: Rare (≥1/10,000, <1/1,000) and very rare (<1/10,000), including isolated reports. Based upon the post-marketing experience, the following adverse reactions have also been reported:

• Metabolism and Nutrition Disorders
  • Very rare: hypokalemia

• Nervous System Disorders
  • Very rare: peripheral neuropathy, headache, and dizziness

• Cardiac Disorders
  • Very rare: congestive heart failure

• Respiratory, Thoracic and Mediastinal Disorders
  • Very rare: pulmonary oedema

• Gastrointestinal Disorders
  • Very rare: abdominal pain, vomiting, dyspepsia, nausea, diarrhoea and constipation

• Hepato-Biliary Disorders
  • Very rare: fatal acute liver failure, serious hepatotoxicity, hepatitis, and reversible increases in hepatic enzymes

• Skin and Subcutaneous Tissue Disorders
  • Very rare: Stevens-Johnson syndrome, angio-oedema, urticaria, alopecia, rash, and pruritus

• Reproductive System and Breast Disorders
  • Very rare: menstrual disorder

• General Disorders and Administrative Site Conditions
  • Very rare: allergic reaction, and oedema

4.9 Overdose
In the event of overdosage, patients should be treated symptomatically with supportive measures. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate. No specific antidote is available. Itraconazole cannot be removed by haemodialysis.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic classification: (Antimycotics for systemic use, triazole derivatives).

ATC code: J02A C02

Itraconazole, a triazole derivative, has a broad spectrum of activity. In vitro studies have demonstrated that itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is a vital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.

For itraconazole, breakpoints have only been established for Candida spp. From superficial mycotic infections (CLSI M27-A2, breakpoints have not been established for EUCAST methodology). The CLSI breakpoints are as follows: susceptible \( \geq 0.125 \); susceptible, dose-dependent 0.25-0.5 and resistant \( \leq 1 \mu g/mL \). Interpretive breakpoints have not been established for the filamentous fungi. In vitro studies demonstrate that itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually \( \leq 1 \mu g/mL \). These include: dermatophytes (Trichophyton spp., Microsporum spp., Epidermophyton floccosum); yeasts (Candida spp., including C. albicans, C. glabrata, Cryptococcus neoformans, Malassezia (formerly Pityrosporum spp., Trichosporon spp., Geotrichum spp.); Aspergillus spp.; Histoplasma spp.; Blastomyces dermatitidis; and various other yeasts and fungi.

Candida glabrata and Candida tropicalis are generally the least susceptible Candida species, with some isolates showing unequivocal resistance to itraconazole in vitro.

The principal fungus types that are not inhibited by itraconazole are Zygomycetes (e.g. Rhizopus spp., Rhizomucor spp., Mucor spp. and Absidia spp.), Fusarium spp., Scedosporium proliferans and Scopulariopsis spp.

Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14α-demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux. Cross resistance between members of the azole class has been observed within Candida spp., although resistance to one member of the class does not necessarily confer resistance to other azoles. Itraconazole-resistant strains of Aspergillus fumigatus have been reported.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of itraconazole has been investigated in healthy subjects, special populations and patients after single and multiple dosing.

Absorption

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

Distribution

Most of the itraconazole in plasma is bound to protein (99.8%) with albumin being the main binding component (99.6% for the hydroxy- metabolite). It has also a marked affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (> 700 L), suggesting its extensive distribution into tissues: Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma. Brain to plasma ratios were about 1 as measured in beagle dogs. The uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma.

Biotransformation

Itraconazole is extensively metabolised by the liver into a large number of metabolites. One of the main metabolites is hydroxy-itraconazole, which has in vitro antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxy-itraconazole are about twice those of itraconazole.

As shown in in vitro studies, CYP 3A4 is the major enzyme that is involved in the metabolism of itraconazole.

Elimination
Itraconazole is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with faeces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas faecal excretion of unchanged drug varies between 3 – 18% of the dose. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

**Linearity/non-linearity**

As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with Cmax and AUC values 4 to 7-fold higher than those seen after a single dose. The mean elimination half-life of itraconazole is about 40 hours after repeated dosing.

**Special Populations**

Hepatic Insufficiency: A pharmacokinetic study using a single 100 mg dose of itraconazole (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC were seen between these two groups. A statistically significant reduction in average Cmax (47%) and a two fold increase in the elimination half-life (37 ± 17 versus 16 ±5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects.

Data are not available in cirrhotic patients during long-term use of itraconazole.

**Renal Insufficiency:** Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when the drug is administered in this patient population.

### 5.3 Preclinical safety data

Subacute and chronic toxicity studies showed undesirable effects of itraconazole in adrenals, liver and ovaries of female rats. Fat metabolism was impaired in rats. Toxic effects occurred at clinical relevant plasma levels. The clinical relevance for the observed effects in animal studies is unknown. Nonclinical data reveal no special hazard based on conventional studies of genotoxicity.

In preclinical studies in male rats, there was a higher incidence of soft-tissue sarcoma at the end of a 2-year treatment. The potential risk for humans is unknown.

There is no evidence of a primary influence on fertility under treatment with itraconazole.

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats and mice at high doses. In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephalocoeles and macroglossia.

A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Core:**
- Sugar Spheres (containing sucrose and maize starch)
- Poloxamer 188
- Hypromellose
- Poloxamer 68 microionised

**Cap:**
- Indigo Carmine (E132)
- Quinoline Yellow (E104)
- Titanium Dioxide (E171)
- Purified water
- Gelatin

**Body:**
- Indigo Carmine (E132)
- Quinoline Yellow (E104)
- Titanium Dioxide (E171)
- Purified water
- Gelatin

#### 6.2 Incompatibilities

Not applicable
6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C
Store in the original package in order to protect from light.

6.5 Nature and contents of container
Aluminium/Aluminium Blister
Pack sizes available:  4, 6, 8, 14, 15, 16, 28, 30, 32, 60, 84 and 90.
                   Hospital packs of 50 (50x1).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Pharmakal Limited
4 Eastbourne Road
Willingdon
Eastbourne
East Sussex
BN20 9LB

8 MARKETING AUTHORISATION NUMBER(S)
PL 20796/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
13/03/2009

10 DATE OF REVISION OF THE TEXT
13/03/2009
PAR Itraconazole 100mg Capsules       UK/H/1317/01/DC

**HINTS AND TIPS**
- **WHEN TO TAKE ITRACONAZOLE CAPSULES**
  - Always take Itraconazole Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
  - Itraconazole Capsules should be swallowed with a glass of water unless your doctor or pharmacist tells you otherwise. The capsule should be ingested whole without slicing or crushing.

**HOW TO TAKE ITRACONAZOLE CAPSULES**
- The following side effects have been reported at the approximate frequencies shown (see also the table below):
  - Headache (dizziness)
  - Nausea, vomiting, feeling sick
  - Diarrhoea
  - Abdominal pain, upset stomach
  - Indigestion
  - Diarrhoea
  - Appetite changes
  - Loss of hair
  - Flushing
  - Skin rash

**HOW TO STORE ITRACONAZOLE CAPSULES**
- Store in a cool and dry place out of the reach and sight of children.

**FURTHER INFORMATION**
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**POSSIBLE SIDE EFFECTS**
- Like all medicines, Itraconazole Capsules can cause side effects, although not everyone gets them.

**STOP TAKING THE CAPSULES**
- If you take more Itraconazole Capsules than you should:
  - If you feel you have taken too many Itraconazole Capsules, contact your nearest hospital casualty department or your doctor immediately. Please take this label with you. If you have taken too many capsules it is important that you tell the hospital or doctor as they may need to take action.

**REMEMBER**
- If you forget to take Itraconazole Capsules DO NOT take a double dose to make up for the forgotten dose.
- Take the next dose as usual. Do not take the next dose sooner than 12 hours after the missed dose (or even if you feel better).

**TREATMENT FOR OVERDOSE**
- If you take too many Itraconazole Capsules:
  - Do not induce vomiting or give any laxatives unless you are told to do so by a doctor or pharmacist.
  - Rinse your mouth out with water and drink plenty of water.

**INFORMATION FOR PHARMACIST**
- Itraconazole Capsules should be stored below 25°C. Do not store in or near the refrigerator.

**MANUFACTURING AUTHORITY AND MANUFACTURER**
- This leaflet was last updated: February 2009.

<table>
<thead>
<tr>
<th>TYPE OF INFECTION</th>
<th>CAPSULES PER DAY</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal candidiasis</td>
<td>2 capsules twice daily</td>
<td>1 day</td>
</tr>
<tr>
<td>Pneumonia virus</td>
<td>2 capsules once daily</td>
<td>7 days</td>
</tr>
<tr>
<td>Ringworm</td>
<td>1 capsule once daily</td>
<td>15 days</td>
</tr>
<tr>
<td>Skin infection of the groin</td>
<td>2 capsules once daily</td>
<td>7 days</td>
</tr>
<tr>
<td>Athletes foot</td>
<td>1 capsule once daily</td>
<td>30 days</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>1 capsule once daily</td>
<td>15 days</td>
</tr>
<tr>
<td>Infections of the nails</td>
<td>2 capsules once daily</td>
<td>5 months</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>1 capsule once daily</td>
<td>15 days</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>2 capsules twice daily</td>
<td>Longer periods depending on response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>YOUR DOCTOR MAY SOMETIMES PRESCRIBE ITRACONAZOLE CAPSULES AT DIFFERENT DOSES OR FOR DIFFERENT LENGTHS OF TIME THAN THOSE ABOVE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>THE TABLE BELOW OUTLINES THE DIRECTIONS TO BE FOLLOWED FOR THE TREATMENT OF YOUR INFECTION. YOUR DOCTOR MAY TELL YOU TO DO SOMETHING DIFFERENT.</td>
</tr>
</tbody>
</table>
Module 4
Labelling

Carton-
Pack size- 4 film coated tablets
Carton-
Pack size- 15 film coated tablets

PAR Itraconazole 100mg Capsules

Each capsule contains 100mg Itraconazole.
Contains sorbitol. See leaflet for further information.

Dosage:
Take as directed by your doctor.
To be taken immediately after a meal.
Please read the enclosed package leaflet before use.

Keep out of the reach and sight of children.

Store in the original package in order to protect from light.

Blister
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Itraconazole 100mg Capsules, in the treatment fungal infections, including yeasts, is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, Itraconazole 100mg Capsules, has been shown to be a generic product of Sporanox 100mg Capsules which was first authorised in Belgium to Janseen-Cilag NV since 1998, over 10 years ago.

Itraconazole belong to a group of medicines called antimycotics for systemic use, also known as “antifungals”, which are used to treat infections caused by fungi including yeasts. Itraconazole Capsules are used to treat fungal infections of the vagina, skin, lungs, mouth, nail and internal organs.

No new preclinical or clinical studies were conducted and none are required for an application of this type. The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, batch release and assembly of this product.

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 of 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 has been reassured that the submitted studies have been carried out in accordance with GCP, and agreed ethical principles.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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.
**II. ABOUT THE PRODUCT**

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Itraconazole 100mg Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antimycotics for systemic use J02AC02</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Capsules, 100mg</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1317/01/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Portugal and Netherlands</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20796/0007</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Pharmakal Limited</td>
</tr>
<tr>
<td></td>
<td>4 Eastbourne Road, Willingdon, East Sussex</td>
</tr>
<tr>
<td></td>
<td>BN20 9LB</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance

General Information
Nomenclature
INN: Itraconazole

Chemical name:

4-[4-[4-[[cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(1RS)-1-methylpropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one.

Molecular formula: C_{35}H_{38}Cl_{2}N_{8}O_{4}
Molecular weight: 706

Physical Properties
Itraconazole is a white or almost white powder, practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in tetrahydrofuran, very slightly soluble in alcohol.

Manufacture
All aspects of the manufacture and control of itraconazole are supported by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability. This certificate is accepted as confirmation of the suitability of itraconazole for inclusion in the medicinal product.

The specification is in compliance with the pharmacopoeia monograph and Certificate of Suitability, with additional tests for bulk density and particle size. The specification of the active substance is satisfactory.

Itraconazole is stored in appropriate packaging that has been evaluated in relation to the grant of the EDQM Certificate of Suitability.

Batch analysis data are provided and comply with the proposed specification.
Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. The data support a re-test period of 5 years when stored in the appropriate packaging at 25°C.

**P Medicinal Product**

Other ingredients consist of pharmaceutical excipients sugar spheres (containing sucrose and maize starch), poloxamer 188, hypromellose, poloxamer 68 microionised. All ingredients within the core of the capsule comply with relevant Ph Eur monographs.

The cap and the body of the capsule contain: indigo carmine (E132), quinoline yellow (E104), titanium dioxide E171, purified water and gelatin. All ingredients within the cap and the body of the capsule comply with relevant Ph Eur monographs.

Satisfactory certificates of analysis have been provided for all excipients. The only excipient used that contains material of animal or human origin is gelatin. A satisfactory TSE certificate of suitability has been provided for the suppliers of gelatin.

**Dissolution and impurity profiles**

Dissolution and impurity profiles of drug product were found to be similar to those for the reference product.

**Manufacture**

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validations of the analytical methods have been presented. Process validation has been carried out on three production scale batches, this is satisfactory. The batch analysis results show that the finished products meet the specifications proposed. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

The product is packaged in blisters composed of aluminium. Specifications and a certificate of analysis for the packaging type used have been provided. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 4, 6, 8, 14, 15, 16, 28, 30, 32, 60, 84 and 90 (hospital packs of 50 (50x1)). Not all pack sizes may be marketed.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory with no specific storage conditions.

**Conclusion**

It is recommended that a Marketing Authorisation is granted for this application.

The proposed product has met the requirements of a generic medicinal product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

**III.2 Non clinical aspects**

No specific non-clinical studies have been performed, which is acceptable for this application for a generic product. Pharmacodynamic, pharmacokinetic and toxicological
properties of itraconazole are well known and further non-clinical studies are not required. A non-clinical overview has been written by a suitably qualified person.

III.3 Clinical aspects

Introduction

To support the application, the applicant has submitted one bioequivalence study, the relative rate and extent of absorption of itraconazole from the two formulations was determined.

Assessor's comment:
As this application concerns a generic medicinal product a bioequivalence study conducted to show that the applicant’s product is essentially similar to the originator is sufficient. No further clinical studies are required for this type of application and applicant has submitted none.

Pharmacokinetics of active ingredient

Peak plasma concentrations of itraconazole are reached 1.5-3 hrs after administration. Under fasting conditions the absolute bioavailability was 55%. Oral intake immediately after a meal doubled the peak levels. 99% of itraconazole is bound to the plasma proteins. The pharmacokinetics of itraconazole is non-linear, after repeated administration itraconazole accumulates in the body. Steady state concentration is reached at day 15, the Cmax 0.5 µg/ml, 1.1 µg/ml and 2.0 µg/ml have been reported after the oral administration of 100mg daily, 200mg daily and 200mg twice daily of itraconazole.
In man the elimination half life is about 20 hrs. At higher doses clearance is reduced due to saturation in liver metabolism.
Peak concentrations of itraconazole in keratinous tissues, especially skin, are up to 3 times higher than in plasma. Therapeutic levels in the skin persist for up to 2-4 weeks after stopping treatment as elimination is related to epidermal regeneration, rather than redistribution into the systemic circulation.
Itraconazole is extensively metabolised by the liver to a large number of metabolites, which constitute 40% of the excreted dose. One of the metabolites, hydroxy-intraconazole, possesses pharmacologic activity similar to the parent compound.
Faecal excretion of parent drug varies from 3-18% of the dose, and urinary excretion of unchanged drug is less than 0.03%.

Biowaiver

NA, single strength.

Bioequivalence study

Study design
Four-period, two-sequence, cross-over, randomized, replicate-design bioequivalence study of single oral doses of Itraconazole/Liconsa 100mg Capsules (Test formulation, Laboratorios Liconsa S.A.-Spain) vs. equal dose reference formulation in healthy male and female volunteers, in fed conditions.
Test and reference products
Test Product (A): Itraconazole / Liconsa 100 mg capsules LABORATORIOS LICONSA S.A., Spain
Certificate of analysis was submitted, the batch size was 538 000 capsules.

Reference Product (B): SPORANOX 100 mg capsules of JANSSEN – CILAG, Spain

Population(s) studied and clinical part of the study
40 healthy volunteers with age range from 18 to 43 years were entered in the study. Inclusion and exclusion criteria were presented. 38 volunteers completed both study phases. Subjects were admitted at the clinical facility in the morning day before study drug administration, subjects remained in the clinical trial site until 24 hours after drug administration. Study drug was administered 30 min after a standardised breakfast with 200 ml water.

Blood samples were collected at pre-dose (0.0) and at 1.0; 2.0; 3.0; 3.5; 4.0; 4.5; 5.0; 5.5; 6.0; 7.0; 8.0; 12.0; 24.0; 36.0; 48.0; 72.0; 96.0 and 120.0 hours post-dose after administration of each product with washout period of 14 days between study periods. A total of six adverse events were reported, mainly mild to moderate in intensity. One study subject experienced three serious adverse events between period 1 and 2 (acute intoxication with CO gas, toxic encephalopatia, convulsive syndrome), not related to the study medication. This subject did not complete the study.

Study was conducted and data analysed according to the clinical trial protocol.

Analytical methods
Plasma concentrations of itraconazole and OH-itraconazole were determined with LC-MS/MS. Plasma samples were prepared using the liquid extraction with acetonitrile. Peak area ratios of the itraconazole and OH-itraconazole to the internal standard (D3-itraconazole) were used from chromatograms and plotted against respective standard concentrations. The calculations of concentrations were performed using weighted (1/x) linear regression models. Analytes stability at various storage conditions was shown. However, itraconazole and OH-itraconazole long term stability in plasma was shown for two weeks, this did not cover the real storage time of study samples (more than 3 months). Matrix effect and method selectivity were shown. Recovery was determined at three concentrations in replicates. Mean recovery for itraconazole was 90% (CV%<10%), for OH-itraconazole 93% (CV%<5%), and for D3-itraconazole 80% (CV%<10%). Dilution integrity 1:4 was shown. All reported plasma concentrations in study samples were within the calibration range.

For itraconazole, calibration curve samples ranged from 2 ng/ml to 400 ng/ml. QC samples were selected at three levels 3 ng/ml, 180 ng/ml, and 360 ng/ml. For OH-itraconazole, calibration curve samples ranged from 3 ng/ml to 600 ng/ml. QC samples were selected at three levels 4 ng/ml, 280 ng/ml, and 560 ng/ml.

All samples collected in the BE study were analysed in 38 analytical sequences. Run acceptance criteria were presented. Back calculated concentrations for the QC samples were submitted and were within the acceptance range indicating within-study accuracy and precision.

Pharmacokinetic Variables and Statistical methods
Pharmacokinetic parameters Cmax, AUC0-t, AUC0-∞, Tmax, T1/2 were determined for all individuals after four period. PK parameters for each individual by treatment and period were tabulated and graphically presented.
SAS version 9.1 and Excel 2003 were used for statistical calculations. The fixed effects of sequence, period and treatment on itraconazole Cmax, AUC0-t and AUC0-inf were evaluated on In-transformed data, using the ANOVA latin-square 2 treatments worksheet of SAS. The 90% confidence interval for the ratio of the population geometric means (Test/Reference) was calculated according to the two one-sided parametric T-test on natural-logarithmic transformed values.

For OH-itraconazole, pharmacokinetic parameters Cmax, AUC0-t, AUC0-inf, were statistically analyzed as for itraconazole.

The bioequivalence acceptance range was set to 80 - 125% for AUC0-t and AUC0-inf, and 75%-133% for Cmax.

**Assessor’s comment**

BE study with replicate design was conducted. The applicant has justified the choice of replicate design with highly variable pharmacokinetics of itraconazole.

EMEA guidance on the Investigation of BA & BE does not address replicate design. According to the FDA guidance on the Statistical Approaches to Establishing BE, generally, replicate design is needed when individual, and not average BE approach, is used to allow estimation of within-subject variances for the test and reference PK parameters.

Average BE approach should be used to establish BE, as set down in the EMEA guidance. Linear mixed effects model procedures are recommended by the FDA for the assessment of average BE in replicate cross-over studies. The fixed effects model with sequence, period and treatment are acceptable for the replicate study with two sequences. Hence, methods of statistical analysis used are acceptable.

Study drug was administered after a standardised breakfast. It is known that the bioavailability of itraconazole doubles when administered with food. BE study under fed conditions is therefore acceptable.

Widened BE limits (0.75-1.33) for Cmax, as pre-specified in the protocol, are acceptable due to the highly variable PK of itraconazole.

None of the pre-dose samples contained detectable levels of itraconazole or OH-itraconazole, length of the washout period was adequate. Blood collection time 120 h was sufficient, area of AUC extrapolated to infinity was less than 20% for all individuals after both treatments.

One of the metabolites, OH-itraconazole has pharmacological activity similar to the parent compound. BE estimation was based on both itraconazole and OH-itraconazole determination in plasma.

**Pharmacokinetic results**

Each subject received both treatments twice. Intra-subject variability calculated from two periods revealed that PK of itraconazole was highly variable after administration of test and reference formulation.

The intra-subject CV% for itraconazole was the following:

AUC0-inf = test - 39%; reference - 52%;
Cmax = test - 37%; reference - 49%.

The intra-subject CV% for OH-itraconazole was the following:
The mean values of within-subject geometric means (arithmetic average for T<sub>max</sub>) for itraconazole and for OH-itraconazole pharmacokinetic parameters are presented below.

The mean pharmacokinetics characteristics of itraconazole after treatment with REFERENCE and TEST products were as follows:

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (hours)</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng/ml*h)</th>
<th>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng/ml*h)</th>
<th>THALF (hours)</th>
<th>Kel (1/hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>72.560</td>
<td>4.467</td>
<td>768.262</td>
<td>835.944</td>
<td>17.790</td>
<td>0.046</td>
</tr>
<tr>
<td>SD</td>
<td>31.791</td>
<td>1.007</td>
<td>387.370</td>
<td>406.497</td>
<td>7.469</td>
<td>0.019</td>
</tr>
<tr>
<td>CV</td>
<td>43.813</td>
<td>22.543</td>
<td>50.422</td>
<td>48.627</td>
<td>41.984</td>
<td>40.882</td>
</tr>
<tr>
<td>Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>71.114</td>
<td>4.724</td>
<td>728.969</td>
<td>793.182</td>
<td>16.160</td>
<td>0.052</td>
</tr>
<tr>
<td>SD</td>
<td>32.594</td>
<td>0.935</td>
<td>395.581</td>
<td>417.803</td>
<td>8.587</td>
<td>0.021</td>
</tr>
<tr>
<td>CV</td>
<td>45.833</td>
<td>19.795</td>
<td>54.266</td>
<td>52.674</td>
<td>53.136</td>
<td>41.101</td>
</tr>
</tbody>
</table>

The mean pharmacokinetics characteristics of OH-itraconazole metabolite after treatment with REFERENCE and TEST products were as follows:

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (hours)</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng/ml*h)</th>
<th>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng/ml*h)</th>
<th>THALF (hours)</th>
<th>Kel (1/hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>161.974</td>
<td>5.138</td>
<td>2166.542</td>
<td>2245.239</td>
<td>7.500</td>
<td>0.097</td>
</tr>
<tr>
<td>SD</td>
<td>63.416</td>
<td>1.112</td>
<td>1102.165</td>
<td>1106.539</td>
<td>1.745</td>
<td>0.021</td>
</tr>
<tr>
<td>Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>156.857</td>
<td>5.369</td>
<td>2109.601</td>
<td>2185.971</td>
<td>7.478</td>
<td>0.098</td>
</tr>
<tr>
<td>SD</td>
<td>64.875</td>
<td>0.739</td>
<td>1250.490</td>
<td>1263.945</td>
<td>2.044</td>
<td>0.022</td>
</tr>
<tr>
<td>CV</td>
<td>41.360</td>
<td>13.757</td>
<td>59.276</td>
<td>57.821</td>
<td>27.331</td>
<td>22.902</td>
</tr>
</tbody>
</table>

Tests of fixed effects for itraconazole showed no significant period and treatment effects on all primary parameters. The significant effects (p<0.05) were found between the sequences for all itraconazole primary parameters. Possibility for carryover effect was analysed in variance analysis, no statistically significant carryover effect was evidenced. None of the predose samples contained measurable levels of itraconazole or its metabolite, indicating that the length of washout period was adequate.
Bioequivalence conclusion.
Ln-transformed values of the PK parameters Cmax, AUC0-t and AUC0-inf were used to calculate the Least Square Means for the test and reference product. Geometric mean ratio of test and reference for each parameter with 90%CI were tabulated.

### Itraconazole

<table>
<thead>
<tr>
<th>Test name</th>
<th>Parameter</th>
<th>Geo Mean Ratio (test/reference)</th>
<th>Lower 90% LL</th>
<th>Upper 90% LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic 90% CI</td>
<td>AUC0-t</td>
<td>92.759</td>
<td>81.885</td>
<td>105.077</td>
</tr>
<tr>
<td>Classic 90% CI</td>
<td>AUC0-inf</td>
<td>92.818</td>
<td>82.404</td>
<td>104.549</td>
</tr>
<tr>
<td>Classic 90% CI</td>
<td>Cmax</td>
<td>96.142</td>
<td>85.905</td>
<td>107.598</td>
</tr>
</tbody>
</table>

### Oh-itraconazole

<table>
<thead>
<tr>
<th>Test name</th>
<th>Parameter</th>
<th>Geo Mean Ratio (test/reference)</th>
<th>Lower 90% LL</th>
<th>Upper 90% LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic 90% CI</td>
<td>AUC0-t</td>
<td>92.075</td>
<td>81.406</td>
<td>104.142</td>
</tr>
<tr>
<td>Classic 90% CI</td>
<td>AUC0-inf</td>
<td>92.269</td>
<td>81.866</td>
<td>103.994</td>
</tr>
<tr>
<td>Classic 90% CI</td>
<td>Cmax</td>
<td>94.544</td>
<td>85.910</td>
<td>104.046</td>
</tr>
</tbody>
</table>

**BIOEQUIVALENCE CONCLUSION**

**Assessor’s comment**

According to the regulatory requirements CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence bioequivalence study should be submitted for the immediate release product to support the application.

Bioequivalence study submitted by the applicant was performed according to the respective NfG and GCP requirements. Replicate study design was used, which is acceptable for highly variable drugs. The statistical methods used to handle the incorporation of within-subject variance component in BE conclusion were acceptable.

The 90% confidence intervals for the ln-transformed AUC and C_{max} for itraconazole and its active metabolite lie within the acceptance criteria of 80-125%.

Therefore, bioequivalence was demonstrated after a single dose (100 mg) administration of two formulations of itraconazole.

**Post-marketing experience and risk-benefit assessment**

No post-marketing data is available. The medicinal product has not been marketed in any country. Itraconazole has a well-recognised efficacy and an acceptable level of safety in the indications approved.
PSUR will be submitted on the date as agreed in the EU harmonised Birthdate initiative. The EU harmonised data lock point was 31st March 2006. The first PSUR for the product will cover the period from grant to the next data lock point. Thereafter PSURs will be submitted on a 3-yearly basis.

Qualified Person for Pharmacovigilance had been nominated and the CV was provided. Description of the applicant’s Pharmacovigilance System was adequate for a generic product since the reference product does not have any identified safety concerns which require additional risk management.

V OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Itraconazole 100mg Capsules 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
Bioequivalence data has been demonstrated between the applicant’s Itraconazole 100mg Capsules and SPORANOX 100 mg capsules of JANSSEN – CILAG, Spain.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The PIL is in compliance with current guidelines and user testing results have been submitted. 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.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with itraconazole is considered to have demonstrated the therapeutic value of the compound. 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>