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.

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Module 1

Product Name	Itraconazole 100mg Capsules
Type of Application	Generic, Article 10.1
Active Substance	Itraconazole
Form	Capsule, hard
Strength	100mg
MA Holder	Pharmakal Limited
RMS	UK
CMS	Portugal and Netherlands
Procedure Number	UK/H/1317/001/DC
Timetable	Day 210 -12/02/2009

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. Dermatophytoses 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:

Indication	***Dose***	***Remarks***
Vulvovaginal candidosis	200mg twice daily for 1 day	
Pityriasis versicolor	200mg once daily for 7 days	
Tinea corporis, tinea cruris	100mg once daily for 15 days or 200mg once daily for 7 days	
Tinea pedis, tinea manuum	100mg once daily for 30 days	
Oropharyngeal candidosis	100mg once daily for 15 days	Increase dose to 200mg once daily for 15 days in AIDS or neutropenic patients because of

Indication	*Dose*	*Remarks*
		impaired absorption in these groups.
Onychomycosis (toenails with or without fingernail involvement)	200 mg once daily for 3 months	

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:

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

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, dofetilide, 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. H_2 -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 other azole 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, dofetilide, 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 methyl prednisolone
- Digoxin
- Others: carbamazepine, cilostazol, 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 pruritis*

•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 ≤ 0.125; susceptible, dose-dependent 0.25-0.5 and resistant ≥ 1µg/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 ≤ 1 µg/ml. These include:
dermatophytes (Trichophyton spp., Microsporum spp., *Epidermophyton floccosum*); yeasts (Candida spp., including *C. albicans*, *C. glabrata, Cryptococcus neoformans*, Malassezia (formely 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 C_{max} (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 encephaloceles 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

Module 3
PATIENT INFORMATION LEAFLET

ITRACONAZOLE
100 mg CAPSULES

PACKAGE LEAFLET: INFORMATION FOR THE USER

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 ITRACONAZOLE CAPSULES ARE AND WHAT THEY ARE USED FOR

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
  - nails
  - internal organs.

2 BEFORE YOU TAKE ITRACONAZOLE CAPSULES

DO NOT take Itraconazole Capsules and talk to your doctor if you are:
- allergic (hypersensitive) to Itraconazole or any of the other ingredients of this medicine
- taking any hay fever antihistamine products containing terfenadine, astemizole or mizolastine
- taking certain medicines used to treat angina (chest pain) and high blood pressure, such as bepridil and nisoldipine
- taking cisapride (a drug used for certain digestive problems)
- taking midazolam (by mouth) or triazolam, medicines taken for anxiety or to help you to sleep (tranquillisers)
- taking certain cholesterol lowering drugs, for example, lovastatin or simvastatin
- taking pimozide or sertindole (drugs for certain conditions affecting thoughts, feelings and/or behaviour)
- taking levacetylmethadol, which is used for the treatment of opioid-dependency
- taking ergot alkaloids (drugs used to treat migraine headaches) such as dihydroergotamine and ergotamine
- taking ergot alkaloids (drugs used after giving birth) such as ergotamine (ergonovine) and methylergometrine (methylergonovine)
- taking certain medicines used to treat irregular heart beat rhythms, e.g. quinidine and dofetilide
- taking eletriptan, which is a drug used to treat migraine headaches.

Take special care with Itraconazole Capsules

Tell your doctor before you start to take this medicine if you have:
- a liver problem, as it may be necessary to adjust your dose of Itraconazole. If your doctor decides to prescribe Itraconazole Capsules, you should be given instructions about potential symptoms that can appear (also read Section 4, Possible side effects). See your doctor if any of the following symptoms appear during your course of treatment with Itraconazole capsules: lack of appetite, feeling sick, vomiting, fatigue, abdominal pain, pale stools or very dark urine. If you have to take Itraconazole Capsules continuously for more than one month, your doctor may ask you for regular blood analysis
- heart problems. If your doctor decides to prescribe Itraconazole Capsules, you should be given instructions about potential symptoms that can appear (also read Section 4, Possible side effects). Inform your doctor immediately if you have wheezing, unexpected weight gain, swelling of the legs or abdomen, unusual fatigue or early insomnia (when you can't fall asleep until very late)
- Acquired Immunodeficiency Syndrome (AIDS) or any condition in which your immune system is not working as well as it should be
- decreased gastric acidity
- a kidney problem, as it may be necessary to adjust your dose of Itraconazole
- suffered an allergic reaction in the past to any other antifungal agent.

You should also tell your doctor immediately, if during treatment with Itraconazole capsules, you experience tingling, numbness or weakness in feet or hands.

Taking other medicines

DO NOT take Itraconazole Capsules if you are taking any of the following medicines:
- any hay fever antihistamine products containing terfenadine, astemizole or mizolastine
- certain medicines for angina or high blood pressure such as bepridil or nisoldipine
- cisapride (a drug used for certain digestive problems)
- midazolam (by mouth) or triazolam, which are medicines taken for anxiety or to help you to sleep (tranquillisers)
- certain cholesterol lowering drugs, for example, lovastatin or simvastatin
- pimozide and sertindole (drugs for certain conditions affecting thoughts, feelings and/or behaviour)
- levacetylmethadol, which is used for the treatment of opioid-dependency
- ergot alkaloids (drugs used to treat migraine headaches) such as dihydroergotamine and ergotamine
- ergot alkaloids (drugs used after giving birth) such as ergotamine (ergonovine) and methylergometrine (methylergonovine)
- eletriptan, which is used to treat migraine headaches
- certain medicines used to treat irregular heart beat rhythms, such as quinidine and dofetilide.

Return to your doctor as soon as possible if you are taking any of these medicines to discuss your treatment.

Some medicines may significantly decrease how well itraconazole works:
- medicines used for the treatment of epilepsy (for example carbamazepine, phenytoin and phenobarbital)
- medicines for the treatment of tuberculosis (for example rifampicin, rifabutin and isoniazid).

Tell your doctor if you are taking any of these medicines in order that adequate measures can be taken.

Combination with some other medicines may require either an adjustment to your dose of Itraconazole Capsules, or to the dose of the other drugs. Examples are:
- certain antibiotics such as clarithromycin, erythromycin and rifabutin
- certain drugs that act on the heart and blood vessels (digoxin, disopyramide and some calcium channel blockers such as dihydropyridines, verapamil and cilostazol)
- drugs that avoid blood coagulation, such as warfarin
- methylprednisolone, budesonide, fluticasone and dexamethasone, which are oral or intravenous use drugs used to treat inflammatory processes, asthma and allergies
- cyclosporin, tacrolimus and rapamycin (also named sirolimus), that are usually given after an organ transplant
- certain antiviral protease inhibitors, such as ritonavir, indinavir and saquinavir
- certain medicines used to treat cancer e.g. busulphan, docetaxel and trimetrexate and vinca alkaloids
- certain medicines used for the treatment of anxiety or to help you sleep (tranquillisers), such as buspirone, alprazolam and brotizolam
- fentanyl, a strong medicine for pain
- atorvastatin, a drug used to lower cholesterol
- halofantrine, a drug used to treat malaria
- repaglinide, a drug used to treat diabetes
- ebastine, a medicine for allergy
- reboxetine, a medicine used to treat depression
- the tranquilliser midazolam when given intravenously
- a painkiller known as alfentanil.

There must be sufficient gastric acidity to assure Itraconazole absorption by the body. Therefore:
- any medicines that neutralise gastric acidity (antacids) should not be taken within two hours before or after taking Itraconazole Capsules
- if you take medicines that stop the production of gastric acid, you should take Itraconazole Capsules with a cola beverage.

Inform your doctor before taking Itraconazole Capsules if any of the above applies to you. Your doctor will then decide whether Itraconazole Capsules are suitable for you. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Important information about some of the ingredients of Itraconazole Capsules
- Patients who are intolerant to **sucrose** should note that Itraconazole Capsules contain a small amount of sucrose. If your doctor has told you that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Taking Itraconazole Capsules with food and drink
- Always take Itraconazole Capsules immediately after a meal as this helps the body absorb the medicine.
- If you are also taking medicines that stop the production of gastric acid, you should take Itraconazole Capsules with a cola beverage.
- DO NOT take alcohol.

Pregnancy and breast-feeding
Pregnancy
- Ask your doctor or pharmacist for advice before taking this or any other medicine
- If you are of child bearing age and could become pregnant, adequate contraceptive precautions should be taken to ensure that you do not become pregnant while you are taking your medicine
- After you stop taking your medicine Itraconazole remains in the body for some time, therefore you should continue to use adequate contraceptive precautions until you have had your next menstrual period.

Breast-feeding
- If you are breast-feeding ask your doctor before taking Itraconazole Capsules, as small amounts of the medicine could be present in your milk.

Driving and using machines
- Taking Itraconazole Capsules is not expected to affect your ability to drive or use machines.

3 HOW 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 you have decreased gastric acid in which case you should swallow with a cola beverage) immediately after a meal.
The usual dose depends on the type and area of infections and is described in the table below:

TYPE OF INFECTION	CAPSULES PER DAY	DURATION
Vaginal infection (thrush)	2 capsules twice daily (2 capsules in the morning and 2 in the evening)	1 day
Pityriasis versicolor	2 capsules once daily	7 days
Skin infection of the groin	2 capsules once daily or 1 capsule once daily	7 days or 15 days
Skin infection of the arms and legs	2 capsules once daily or 1 capsule once daily	7 days or 15days
Athletes foot	1 capsule once daily	30 days
Skin infection of the hand	1 capsule once daily	30 days
Infections of the mouth	1 capsule once daily	15 days
Infections of the nails	2 capsules once daily	3 months
Internal infections	200 mg once or twice daily	Longer periods depending on response

Your doctor may sometimes prescribe Itraconazole Capsules at different dosages or for different lengths of time than those shown above.
It is important that you carry on taking your medicine for as long as your doctor has told you to. This will help to prevent your infection returning. DO NOT stop your treatment just because you feel better. Talk to your doctor if this applies to you.
In skin infections, the lesions will disappear a few weeks after finishing the treatment. This is characteristic of the spots produced by the fungus. Although itraconazole kills the fungus, the lesion does not disappear until new skin has grown. Similarly, lesions on the nails will disappear 6 to 9 months after finishing your treatment. Therefore, do not worry if you don't notice an improvement during the treatment. Always follow your doctor's advice.

If you take more Itraconazole Capsules than you should
If you (or someone else) swallow a lot of the capsules all together or if you think a child has swallowed any of the capsules, contact your nearest hospital casualty department or your doctor immediately. Please take this leaflet, any remaining capsules and the container with you to the hospital or doctor so that they know which capsules were consumed.

If you forget to take Itraconazole Capsules
DO NOT take a double dose to make up for a forgotten capsule. Take the next dose as usual and continue your course until the capsules are finished.

4 POSSIBLE SIDE EFFECTS

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

Stop taking the capsules and tell your doctor immediately or go to the casualty department at your nearest hospital if the following happens:
- an allergic reaction (swelling of the lips, face or neck leading to severe difficulty in breathing; skin rash or hives).

This is a very serious but rare side effect. You may need urgent medical attention or hospitalisation.

Stop taking the capsules and contact your doctor immediately if you experience any of the following effects:
- lack of appetite, nausea (feeling sick), vomiting (being sick), tiredness, abdominal pain, muscle weakness, jaundice (yellowing of the skin), very dark urine, pale stools and hair loss have occurred. These may be signs that the medicine is affecting your liver
- a tingling sensation, numbness or weakness in the limbs or a severe skin disorder. These occur very rarely.

See or let your doctor know immediately if you experience:
- shortness of breath, unexpected weight gain, swelling of the legs or abdomen, unusual fatigue or begin to wake up at night. These may be signs of heart failure reactions which have been reported rarely.

The following side effects have been reported at the approximate frequencies shown:
Very rare (affecting less than one person in 10,000):
- headache, dizziness
- nausea (feeling sick), vomiting (being sick)
- diarrhoea
- abdominal pain, upset stomach
- indigestion
- constipation
- changes in menstrual bleeding
- muscle weakness
- hair loss
- low blood levels of potassium.

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.

5 HOW TO STORE ITRACONAZOLE CAPSULES

Keep out of the reach and sight of children.
Do not store above 25°C. Store in the original package in order to protect from light.
Do not use Itraconazole Capsules after the expiry date that is stated on the outer packaging. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What Itraconazole Capsules contain:
- The active substance is itraconazole. Each capsule contains 100 mg itraconazole.
- The other ingredients are sugar spheres (maize starch and sucrose 224.31 mg per capsule), poloxamer 188 and poloxamer 68, hypromellose. The capsule shells consist of indigo carmine (E132), quinoline yellow (E104), titanium dioxide (E171), purified water and gelatin.

What Itraconazole Capsules look like and contents of the pack:
- Itraconazole 100 mg Capsules are hard gelatin capsules (size 0) with a green opaque cap and body containing yellowish-beige spherical microgranules.
- Itraconazole 100 mg Capsules are available in pack sizes of 4, 6, 8, 14, 15, 16, 28, 30, 32, 60, 84 and 90, and hospital packs of 50 (50x1).
  Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder
Pharmakal Limited, East Sussex, BN20 9LB.

Manufacturer
Laboratorios Liconsa, S.A.,
Avda. Miralcampo, No 7,
Polígono Industrial Miralcampo
19200 Azuqueca de Henares (Guadalajara),
Spain.

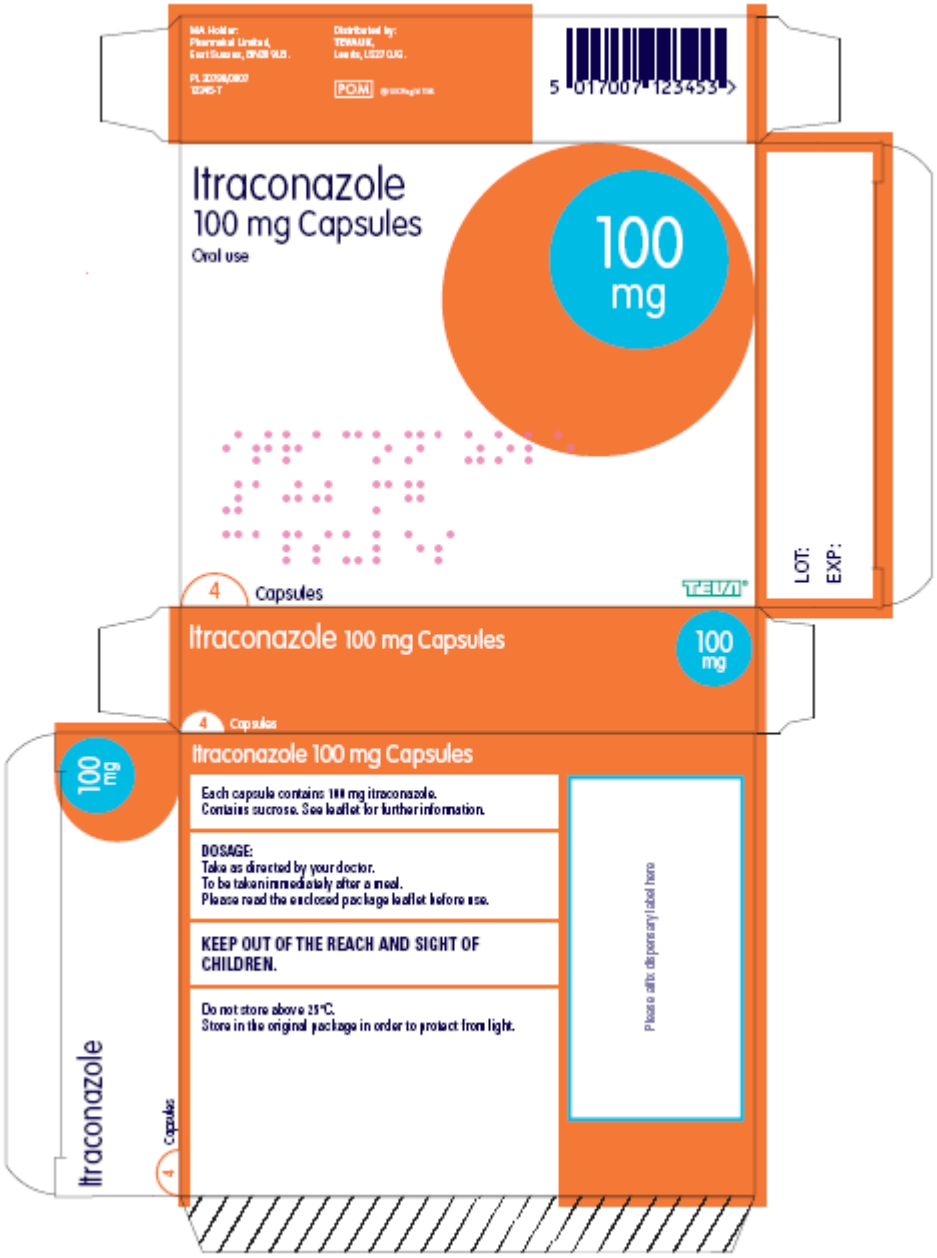
This leaflet was last revised:
February 2009.

PL 20796/0007

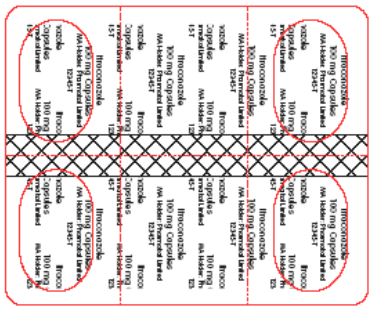
TEVA UK LIMITED 12345-T

Module 4
Labelling

Carton-
Pack size- 4 film coated tablets

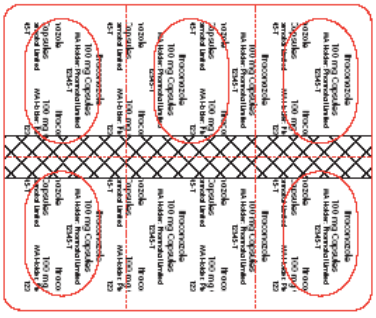


Blister



Carton-
Pack size- 15 film coated tablets

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.

Itraconzole 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

Name of the product in the Reference Member State	Itraconazole 100mgCapsules
Name(s) of the active substance(s) (INN)	Itraconazole
Pharmacotherapeutic classification (ATC code)	Antimycotics for systemic use J02AC02
Pharmaceutical form and strength(s)	Capsules, 100mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1317/01/DC
Reference Member State	United Kingdom
Member States concerned	Portugal and Netherlands
Marketing Authorisation Number(s)	PL 20796/0007
Name and address of the authorisation holder	Pharmakal Limited 4 Eastbourne Road, Willingdon, East Sussex BN20 9LB United Kingdom

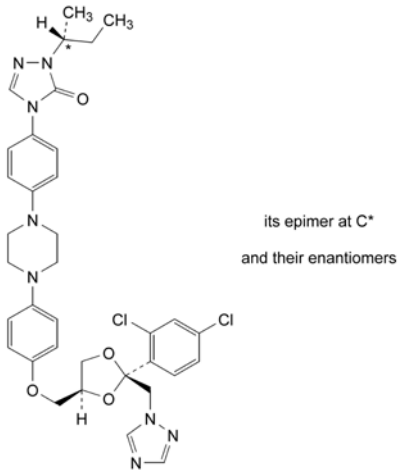
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance

General Information
Nomenclature
INN: Itraconazole

Chemical name:

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

Molecular formula: $C_{35}H_{38}Cl_2N_8O_4$
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^{o}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 absoulte 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 itraconasole 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 compelete 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 ln-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:

AUC0-inf= test - 42%; reference - 48%;
Cmax = test - 34%; reference - 38%.

The mean values of within-subject geometric means (arithmetic average for Tmax) 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:

Reference treatment

	Cmax (ng/ml)	Tmax (hours)	AUC0-t (ng/ml*h)	AUC0-inf (ng/ml*h)	THALF (hours)	Kel (1/hours)
Mean	72.560	4.467	768.262	835.944	17.790	0.046
SD	31.791	1.007	387.370	406.497	7.469	0.019
CV	43.813	22.543	50.422	48.627	41.984	40.882

Test treatment

	Cmax (ng/ml)	Tmax (hours)	AUC0-t (ng/ml*h)	AUC0-inf (ng/ml*h)	THALF (hours)	Kel (1/hours)
Mean	71.114	4.724	728.969	793.182	16.160	0.052
SD	32.594	0.935	395.581	417.803	8.587	0.021
CV	45.833	19.795	54.266	52.674	53.136	41.101

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

Reference treatment

	Cmax (ng/ml)	Tmax (hours)	AUC0-t (ng/ml*h)	AUC0-inf (ng/ml*h)	THALF (hours)	Kel (hours)
Mean	161.974	5.138	2166.542	2245.239	7.500	0.097
SD	63.416	1.112	1102.165	1106.639	1.745	0.021
CV	39.152	21.633	50.872	49.288	23.261	21.274

Test treatment

	Cmax (ng/ml)	Tmax (hours)	AUC0-t (ng/ml*h)	AUC0-inf (ng/ml*h)	THALF (hours)	Kel (hours)
Mean	156.857	5.369	2109.601	2185.971	7.478	0.098
SD	64.875	0.739	1250.490	1263.945	2.044	0.022
CV	41.360	13.767	59.276	57.821	27.331	22.902

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

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

Oh-itraconazole

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

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

Date submitted	Application type	Scope	Outcome