# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

ITRACONAZOLE 100 mg Capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg itraconazole.

Excipient(s) with known effect: Sucrose 224.31 mg per capsule.
For the 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

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 | 200 mg twice daily for 1 day | |
| Pityriasis versicolor | 200 mg once daily for 7 days | |
| Tinea corporis, tinea cruris | 100 mg once daily for 15 days or<br>200 mg once daily for 7 days | |
| Tinea pedis, tinea manuum | 100 mg once daily for 30 days | |
| Oropharyngeal candidosis | 100 mg once daily for 15 days | Increase dose to<br>200 mg once daily<br>for 15 days in AIDS<br>or neutropenic<br>patients because of impaired absorption<br>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<br><br>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<br><br>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.

*Paediatric population*

Not recommended. See 4.4 Special warnings and special precautions for use.

In older people: 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

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

Itraconazole is contra-indicated in patients who have shown hypersensitivity to the drug or its excipients.

Co-administration 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. 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 atorvastatin, 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.

Itraconazole must not be used during pregnancy (except for life-threatening cases). See section ‘Fertility, pregnancy and lactation‘.

Women of childbearing potential taking itraconazole should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of itraconazole therapy.

## 4.4. Special warnings and special precautions for use

*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.

*Cardiac effects*

- In a healthy volunteer study with Itraconazole intravenous, a transient asymptomatic decrease of the left ventricular ejection fraction was observed, this resolved before the next infusion. The clinical relevance of these findings to the oral formulations is unknown.

- 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 dosing regimen (e.g., total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. 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 used 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).

Itraconazole should not be used within 2 weeks after discontinuation of treatment with CYP3A4 inducing agents (rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine, Hvpericum perforatum (St. John's Wort)). The use of itraconazole with these drugs may lead to subtherapeutic plasma levels of itraconazole and thus treatment failure.

*Reduced gastric acidity*:

- Absorption of itraconazole from itraconazole capsules 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 capsules. 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.

*Paediatric population*

- 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 older people*

- Clinical data on the use of Itraconazole capsules in older 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. Most of these cases 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. Some patients had no obvious risk factors for liver disease. Some of these cases were 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 should be conducted. 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. Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population.

*Renal impairment*

Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population. The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. Dose adaptation may be considered.

*Hearing loss*

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see sections 'Contraindications' and 'Interaction with other medicinal products and other forms of interaction'). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

*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-resistance*

- 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.

*Disorders of carbohydrate metabolism*

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 enzyme 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, *hypericum perforatum* (St.John's Wort), 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 atorvastatin, 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 due to an increased risk of CHF. 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 (via inhibition of P-glycoprotein)
- 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 zidovudine (AZT) 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 sulfamethazine.

## 4.6. Fertility, pregnancy and lactation

*Women of child-bearing potential*

Women of childbearing potential taking itraconazole should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of itraconazole therapy.

*Pregnancy*
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.

In animal studies itraconazole has shown reproduction toxicity.

There is limited information on the use of itraconazole during pregnancy. During postmarketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations. A causal relationship with itraconazole has not been established.

Epidemiological data on exposure to itraconazole during the first trimester of pregnancy - mostly in patients receiving short-term treatment for vulvovaginal candidosis - did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.

*Breast-feeding*
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

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbance and hearing loss (see section 4.8), which may occur in some instances, must be taken into account.

## 4.8. Undesirable effects

Undesirable effects listed below have been reported in clinical trials with itraconazole capsules and/or from spontaneous reports from post-marketing experience for all itraconazole formulations.

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%).

In clinical trials involving 2,104 itraconazole-treated patients in the treatment of dermatomycoses or onychomycosis, the most frequently reported adverse experiences in clinical trials were of gastrointestinal, hepatic and dermatological origin.

**List of adverse reactions**
The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare ( >1/10,000 to <1/1,000), very rare (<1/10,000; including isolated reports), not known (cannot be estimated from the available data).

*Blood and lymphatic system disorders*
***Rare:*** *leucopenia*
*Not known* *neutropenia, thrombocytopenia*

*Immune system disorders*
Uncommon: hypersensitivity
Not known: anaphylactic reaction, anaphylactoid reaction, angioneurotic oedema, serum sickness

*Metabolism and nutrition disorders*
Very rare: hypokalemia
Not known: hypertriglyceridemia

*Nervous system disorders*
Uncommon: headache, dizziness, paraesthesia
Rare: hypoaesthesia
Very rare**:** peripheral neuropathy

*Eye disorders*
Rare: visual disturbance
Not known: vision blurred and diplopia

*Ear and labyrinth disorders*
Rare: tinnitus
Not known: transient or permanent hearing loss

*Cardiac disorders*
Very rare: congestive heart failure

*Respiratory, thoracic and mediastinal disorders*
Very rare: pulmonary oedema

*Gastrointestinal disorders*
Common: abdominal pain,nausea
Uncommon: vomiting, diarrhoea, constipation, dyspepsia, dysgeusia; flatulence
Rare: pancreatitis

*Hepatobiliary disorders*

| | |
|---|---|
| Uncommon: | hyperbilirubinaemia, alanine aminotransferase increased, aspartate aminotransferase increased |
| Rare: | hepatic enzyme increased |
| Very rare: | fatal acute hepatic failure, hepatitis, serious hepatotoxicity |

*Skin and subcutaneous tissue disorders*

| | |
|---|---|
| Common: | rash |
| Uncommon: | urticaria, alopecia, pruritus |
| Very rare: | Stevens-Johnson syndrome, angio-oedema |
| Not known: | toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, photosensitivity |

*Musculoskeletal and connective tissue disorders*

| | |
|---|---|
| Not known: | myalgia, arthralgia |

*Renal and urinary disorders*

| | |
|---|---|
| Rare: | pollakiuria |
| Not known: | urinary incontinence |

*Reproductive system and breast disorders*

| | |
|---|---|
| Uncommon: | menstrual disorder |
| Not known: | erectile dysfunction |

*General disorders and administrative site conditions*

| | |
|---|---|
| Uncommon: | oedema |
| Rare: | pyrexia |
| Very rare: | allergic reaction |

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

### 4.9. Overdose

No data are available.
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 group: (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 (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 $AUC_{\infty}$ 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 the 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

TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG

## 8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1357

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

13/03/2009

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03/06/2015