# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Itraconazole 100 mg capsules, hard

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 100 mg itraconazole.
Excipient: sucrose
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard

Size 0, filled with white to off white pellets. Capsule cap: white, opaque.
Capsule body: white, opaque.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Superficial mycoses*

Itraconazole is indicated – if external treatment is not effective or not appropriate – for the treatment of the following fungal infections:

- dermatomycoses (e.g. tinea corporis, tinea cruris, tinea pedis, tinea manus)
- *Pityriasis versicolor*

***Systemic mycoses***

Itraconazole is indicated for the treatment of systemic mycoses, such as candidiasis, aspergillosis, and histoplasmosis.

Consideration should be given to official guidance on the appropriate use of antimycotic agents.

## 4.2 Posology and method of administration

Posology

| Superficial mycoses (of skin, mucosae) | | |
|---|---|---|
| **Indication** | **Dosage** | **Duration of treatment** |
| **Tinea corporis, Tinea cruris** | 1 capsule once daily (equivalent to 100 mg itraconazole) | 2 weeks |
| **Dermatomycosis of palms and soles (tinea manus, tinea pedis)** | 1 capsule once daily (equivalent to 100 mg itraconazole) | 4 weeks |
| ***Pityriasis versicolor*** | 2 capsules once daily (equivalent to 200 mg itraconazole) | 7 days |
| In some immunosuppressed patients, e.g. with neutropenia, AIDS or after organ transplantation, the bioavailability of itraconazole may be lowered. Doubling the dose may be indicated. | | |

Itraconazole remains substantially longer in the skin than in the blood.
Optimal healing is thus achieved 2-4 weeks after withdrawing Itraconazole in case of mycoses of the skin.

| Systemic mycoses | | | |
|---|---|---|---|
| **Indication** | **Dosage** | **Duration of treatment[1)]** | **Notes** |
| **Aspergillosis** | 2 capsules once daily (equivalent to 200 mg itraconazole) | 2-5 months | In invasive or disseminated disease, increase to 2 capsules twice daily (in the morning and in the evening) (equivalent to 400 mg itraconazole) |
| **Candidiasis** | 1-2 capsules once daily (equivalent to 100-200 mg itraconazole) | 3 weeks-<br>7 months | In invasive or disseminated disease, increase to 2 capsules twice daily (in the morning and in the evening) (equivalent to 400 mg itraconazole) |
| **Histoplasmosis** | 2 capsules once daily up to twice | 8 months | |

| | | | |
|---|---|---|---|
| | daily (in the morning and in the evening) (equivalent to 200-400 mg itraconazole) | | |

[1)] The duration of treatment should be adjusted depending on clinical efficacy.

*Paediatric population*

Since clinical data on the use of itraconazole in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks (see section 4.4).

Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes (see section 4.8).

*Use in older patients*

Since clinical data on the use of itraconazole in older patients is limited, its use in older patients is not recommended unless the potential benefit outweighs the potential risks (see section 4.4).

*Use in patients with impaired renal function*

The oral bioavailability of itraconazole may be reduced in patients with renal insufficiency. Dose adjustment should be taken into consideration (see section 4.4).

*Use in patients with impaired hepatic function*

Itraconazole is predominantly metabolized in the liver. In patients with hepatocirrhosis, the terminal half-life of itraconazole is somewhat prolonged and the oral bioavailability of itraconazole somewhat reduced. Dose adjustment should be taken into consideration (see section 4.4).

Method of administration

The capsules are to be taken without chewing with some liquid directly after a meal in order to achieve maximum absorption.

## 4.3 Contraindications

Itraconazole is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration of a number of CYP3A4 substrates is contraindicated with itraconazole. Increased plasma concentrations of these active ingredients, caused by coadministration with itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. For example, increased plasma concentrations of some of these active ingredients can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Specific examples are listed in section 4.5.

- Itraconazole 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 section 4.4).
- Itraconazole must not be used during pregnancy, except for life-threatening cases (see section 4.6).
- 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 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 capsules to patients with hypersensitivity to other azoles.

*Cardiac effects*
In a healthy volunteer study with intravenous itraconazole, 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 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 exercised when coadministering itraconazole and calcium channel blockers (see section 4.5) due to an increased risk of congestive heart failure.

*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 medicinal products. 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.

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the medicinal product is administered in this patient population. It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolised by CYP3A4.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other medicinal products, treatment with itraconazole is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications (see section 5.2).

*Reduced gastric acidity*
Absorption of itraconazole from itraconazole capsules is impaired when gastric acidity is reduced. In patients with reduced gastric acidity, whether from disease (e.g. patients with achlorhydria) or from concomitant medication (e.g. patients taking medicinal products that reduce gastric acidity), it is advisable to administer itraconazole capsules with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary (see section 4.5).

*Paediatric population*

Clinical data on the use of itraconazole capsules in paediatric patients is limited. The use of itraconazole capsules in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.

*Use in older patients*
Clinical data on the use of itraconazole capsules in older patients is limited. It is advised to use itraconazole capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an older patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or therapy with other medicinal products.

*Renal impairment*
Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal Insufficiency. Caution should be exercised when this medicinal product is administered in this patient population and adjusting the dose 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 section 4.5). 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, the treatment should be discontinued.

*Cross-resistance*

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.

*Interchangeability*
It is not recommended that itraconazole capsules and itraconazole oral solution be used interchangeably. This is because itraconazole exposure is greater with the oral solution than with the capsules when the same dose of the active ingredient is given.

*Interaction potential*
Coadministration of specific medicinal products with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered medicinal product, life-threatening effects and/or sudden death. Active ingredients that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in section 4.5.

*Disorders of carbohydrate metabolism*
This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or saccharase-isomaltase deficiency should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

Itraconazole is mainly metabolised through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Similarly, itraconazole may modify the pharmacokinetics of other substances that share this metabolic pathway. Itraconazole is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. When using concomitant medication, it is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust dosages.

**Medicinal products that may decrease itraconazole plasma concentrations**
Medicinal products that reduce the gastric acidity (e.g. acid neutralising medicines such as aluminum hydroxide, or acid secretion suppressors such as $H_2$-receptor antagonists and proton pump inhibitors) impair the absorption of itraconazole from itraconazole capsules. It is recommended that these medicinal products be used with caution when coadministered with itraconazole capsules.

It is recommended that itraconazole be administered with an acidic beverage (such as non-diet cola) upon co-treatment with medicinal products reducing gastric acidity.

It is recommended that acid neutralising medicines (e.g. aluminum hydroxide) be administered at least 1 hour before or 2 hours after the intake of itraconazole capsules.

Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Coadministration of itraconazole with potent enzyme inducers of CYP3A4 may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be largely reduced. Examples include:

Antibacterials: isoniazid, rifabutin (see also under section “Medicinal products that may have their plasma concentrations increased by itraconazole”), rifampicin.

Anticonvulsants: carbamazepine, (see also under section “Medicinal products that may have their plasma concentrations increased by itraconazole”), phenobarbital, phenytoin.

Antivirals: efavirenz, nevirapine.

Therefore, administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these medicinal produts be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy.

Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

**Medicinal products that may increase itraconazole plasma concentrations**
Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole. Examples include:
Antibacterials: ciprofloxacin, clarithromycin, erythromycin
Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir (see also under section “Medicinal products that may have their plasma concentrations increased by itraconazole”), ritonavir (see also under section “Medicinal products that may have their plasma concentrations increased by itraconazole”).

It is recommended that these medicinal products be used with caution when coadministered with itraconazole capsules. It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured.

**Medicinal products that may have their plasma concentrations increased by itraconazole**
Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of active ingredients metabolised by CYP3A4 and can inhibit the transport of active ingredients by P-glycoprotein, which may result in

increased plasma concentrations of these active ingredients and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these medicinal products. CYP3A4-metabolised active ingredients known to prolong the QT interval may be contraindicated with itraconazole, since the combination may lead to ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors, the decline in plasma concentrations may be even more gradual. This is particularly important when initiating therapy with active ingredients whose metabolism is affected by itraconazole.

The interacting medicinal products are categorized as follows:

- 'Contraindicated': Under no circumstances is the medicinal product to be coadministered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.
- 'Not recommended': It is recommended that the use of the medicinal product be avoided during and up to two weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting medicinal product is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured.
- 'Use with caution': Careful monitoring is recommended when the medicinal product is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting medicinal product, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured.

Examples of active ingredients that may have their plasma concentrations increased by itraconazole presented by class of active ingredient with advice regarding coadministration with itraconazole:

| **Class of active ingredient** | **Contraindicated** | **Not recommended** | **Use with caution** |
|---|---|---|---|
| Alpha Blockers | | tamsulosin | |
| Analgesics | levacetylmethadol (levomethadyl), methadone | fentanyl | alfentanil, buprenorphine IV and sublingual, oxycodone |
| Antiarrhythmics | disopyramide, dofetilide, dronedarone, quinidine | | digoxin |
| Antibacterials | | rifabutin[a] | |

| **Class of active ingredient** | **Contraindicated** | **Not recommended** | **Use with caution** |
|---|---|---|---|
| Anticoagulants and antiplatelet medicinal products | | rivaroxaban | coumarins, cilostazol, dabigatran |
| Anticonvulsants | | carbamazepine[a] | |
| Antidiabetics | | | repaglinide, saxagliptin |
| Antihelmintics and antiprotozoals | halofantrine | | praziquantel |
| Antihistamines | astemizole, mizolastine, terfenadine | | ebastine |
| Antimigraine medicinal products | ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine) | | eletriptan |
| Antineoplastics | irinotecan | dasatinib, nilotinib, trabectedin | bortezomib, busulphan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids |
| Antipsychotics, anxiolytics and hypnotics | lurasidone, oral midazolam, pimozide, sertindole, triazolam | | alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone |
| Antivirals | | | maraviroc, indinavir[b], ritonavir[b], saquinavir |
| Beta Blockers | | | nadolol |
| Calcium Channel Blockers | bepridil, felodipine, lercanidipine, nisoldipine | | other dihydropyridines, including verapamil |

| Class of active ingredient | Contraindicated | Not recommended | Use with caution |
|---|---|---|---|
| Cardiovascular medicinal products, miscellaneous | ivabradine, ranolazine | aliskiren | |
| Diuretics | eplerenone | | |
| Gastrointestinal medicinal products | cisapride | | aprepitant, domperidone |
| Immunosuppressants | | everolimus | budesonide, ciclesonide, ciclosporin, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus |
| Lipid regulating medicinal products | lovastatin, simvastatin | | atorvastatin |
| Respiratory medicinal products | | salmeterol | |
| SSRIs, tricyclics and related antidepressants | | | reboxetine |
| Urological medicinal products | | vardenafil | fesoterodine. imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine |
| Other | colchicine, in subjects with renal or hepatic impairment | colchicine | alitretinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan |

[a] See also under section "Medicinal products that may decrease itraconazole plasma concentrations"
[b] See also under section "Medicinal products that may increase itraconazole plasma concentrations"

**Medicinal products that may have their plasma concentrations decreased by itraconazole**

Coadministration of itraconazole with the NSAID meloxicam may decrease the plasma concentrations of meloxicam. It is recommended that meloxicam be used with caution when coadministered with itraconazole, and its effects or

side effects be monitored. It is recommended that the dosage of meloxicam, if coadministered with itraconazole, be adapted if necessary.

Paediatric population
Interaction studies have only been performed in adults.

## 4.6 Pregnancy and lactation

*Pregnancy*
Itraconazole 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 (see section 4.3).

In animal studies itraconazole has shown reproduction toxicity (see section 5.3).

There is limited information on the use of itraconazole during pregnancy. During post-marketing 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.

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

*Breast-feeding*
A very small amount of itraconazole is excreted in human milk. The expected benefits of itraconazole capsules therapy should therefore be weighed against the potential risk of breast-feeding. In case of doubt, the patient should not breast-feed.

*Fertility*
There was no evidence of a primary influence on fertility based on preclinical safety data (see section 5.3).

## 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 disturbances and hearing loss (see section 4.8), which may occur in some instances, must be taken into account.

## 4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) with itraconazole capsules treatment identified from clinical trials and/or from spontaneous reporting were headache, abdominal pain, and nausea. The most serious ADRs were serious allergic reactions, cardiac failure/congestive heart failure/pulmonary oedema, pancreatitis, serious hepatotoxicity (including some cases of fatal acute liver failure), and serious skin reactions. Refer to subsection "Tabulated list of adverse reactions" for the frequencies and for other observed ADRs. Refer to section 4.4 for additional information on other serious effects.

Tabulated list of adverse reactions

The ADRs in the table below were derived from open-label and double-blind clinical trials with itraconazole capsules involving 8499 patients in the treatment of dermatomycoses or onychomycosis, and from spontaneous reporting.

The table below presents ADRs by System Organ Class. Within each System Organ Class, the ADRs are presented by incidence, using the following convention:

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)
Not known (cannot be estimated from the available data)

| **System Organ Class** | **Common** ≥ 1/100 to < 1/10 | **Uncommon** ≥ 1/1000 to < 1/100 | **Rare** ≥ 1/10 000 to < 1/1000 |
|---|---|---|---|
| **Infections and infestations** | | Sinusitis, upper respiratory tract infection, rhinitis | |
| **Blood and lymphatic system disorders** | | | Leukopenia |
| **Immune system disorders** | | Hypersensitivity* | Serum sickness, angioneurotic oedema, anaphylactic reaction |

| **System Organ Class** | **Common** ≥ 1/100 to < 1/10 | **Uncommon** ≥ 1/1000 to < 1/100 | **Rare** ≥ 1/10 000 to < 1/1000 |
|---|---|---|---|
| **Metabolism and nutrition disorders** | | | Hypertriglyceridemia |
| **Nervous system disorders** | Headache | | Hypoaesthesia, paraesthesia, dysgeusia |
| **Eye disorders** | | | Visual disturbance (including diplopia and blurred vision) |
| **Ear and labyrinth disorders** | | | Transient or permanent hearing loss*, tinnitus |
| **Cardiac disorders** | | | Congestive heart failure* |
| **Respiratory, thoracic and mediastinal disorders** | | | Dyspnoea |
| **Gastrointestinal disorders** | Abdominal pain, nausea | Vomiting, diarrhoea, constipation, dyspepsia, flatulence | Pancreatitis |
| **Hepatobiliary disorders** | | Hepatic function abnormal | Serious hepatotoxicity (including some cases of fatal acute liver failure)*, hyperbilirubinaemia |
| **Skin and subcutaneous tissue disorders** | | Urticaria, rash, pruritus | Toxic epidermal necrolysis, Stevens-Johnson Syndrome, acute generalised exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, alopecia, photosensitivity |
| **Renal and urinary disorders** | | | Pollakiuria |

| System Organ Class | Common ≥ 1/100 to < 1/10 | Uncommon ≥ 1/1000 to < 1/100 | Rare ≥ 1/10 000 to < 1/1000 |
|---|---|---|---|
| **Reproductive system and breast disorders** | | Menstrual disorder | Erectile dysfunction |
| **General disorders and administration site conditions** | | | Oedema |
| **Investigations** | | | Blood creatine phosphokinase increased |

* see section 4.4.

Description of selected adverse reactions
The following is a list of ADRs associated with itraconazole that have been reported in clinical trials of itraconazole oral solution and intravenous itraconazole, excluding the ADR term "Injection site inflammation", which is specific to the injection route of administration.

| | |
|---|---|
| **Blood and lymphatic system disorders** | Granulocytopenia, thrombocytopenia |
| **Immune system disorders** | Anaphylactoid reaction |
| **Metabolism and nutrition disorders** | Hyperglycaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia |
| **Psychiatric disorders** | Confusional state |
| **Nervous system disorders** | Peripheral neuropathy*, dizziness, somnolence, tremor |
| **Cardiac disorders** | Cardiac failure, left ventricular failure, tachycardia |
| **Vascular disorders** | Hypertension, hypotension |
| **Respiratory, thoracic and mediastinal disorders** | Pulmonary oedema, dysphonia, cough |
| **Gastrointestinal disorders** | Gastrointestinal disorder |
| **Hepatobiliary disorders** | Hepatic failure*, hepatitis, jaundice |
| **Skin and subcutaneous tissue disorders** | Rash erythematous, hyperhidrosis |
| **Musculoskeletal and connective tissue disorders** | Myalgia, arthralgia |

| | |
|---|---|
| **Renal and urinary disorders** | Renal impairment, urinary incontinence |
| **General disorders and administration site conditions** | Generalised oedema, face oedema, chest pain, pyrexia, pain, fatigue, chills |
| **Investigations** | Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, blood urea increased, gamma-glutamyltransferase increased, hepatic enzyme increased, urine analysis abnormal |

Paediatric population
The safety of itraconazole oral solution was evaluated in 250 paediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least one dose of itraconazole oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data. Based on pooled safety data from these clinical trials, the very common reported ADRs in paediatric patients were vomiting (36.0%), pyrexia (30.8%), diarrhoea (28.4%), mucosal inflammation (23.2%), rash (22.8%), abdominal pain (17.2%), nausea (15.6%), hypertension (14.0%), and cough (11.2%). The nature of ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric patients.

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: www.mhra.gov.uk/yellowcard.

## 4.9 Overdose

Symptoms and signs
In general, adverse events reported with overdose have been consistent with those reported for itraconazole use (see section 4.8).

Treatment
In the event of overdose, supportive measures should be employed. Activated charcoal may be given if considered appropriate.

Itraconazole cannot be removed by haemodialysis.
No specific antidote is available.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivative.
*ATC code*: J02AC02

Mechanism of action
Itraconazole inhibits fungal 14α-demethylase, resulting in a depletion of ergosterol and disruption of membrane synthesis by fungi.

Pharmacokinetic/pharmacodynamic relationship
The PK/PD relationship for itraconazole, and for triazoles in general, is poorly understood and is complicated by limited understanding of antifungal pharmacokinetics.

Mechanisms of resistance
Resistance of fungi to azoles appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are:

- Over-expression of *ERG11*, the gene that encodes 14-alpha-demethylase (the target enzyme)
- Point mutations in *ERG11* that lead to decreased affinity of 14-alpha-demethylase for itraconazole
- Drug-transporter over-expression resulting in increased efflux of itraconazole from fungal cells (i.e., removal of itraconazole from its target)
- Cross-resistance. Cross-resistance amongst members of the azole class of active ingredients has been observed within *Candida* species though resistance to one member of the class does not necessarily confer resistance to other azoles.

Breakpoints
Using EUCAST methods, breakpoints for itraconazole have only been established for aspergillus species. These breakpoints are given in the table below, according to EUCAST Antifungal Clinical Breakpoint Table v. 4.1, valid from 2012-03-05)

| Antifungal agent | Species-related breakpoints (S≤/R>) (mg/L) | | | | | Non-species related breakpoints S≤/R> |
|---|---|---|---|---|---|---|
| | *A. flavus* | *A. fumigatus* | *A. nidulans* | *A. niger* | *A. terreus* | |
| Itraconazole[1] | 1/2 | 1/2 | 1/2 | IE[2,3] | 1/2 | IE[3] |

A. = Aspergillus

S = Susceptible, R = Resistant

1. Monitoring of itraconazole trough concentrations in patients treated for fungal infection is recommended.
2. The ECOFFs for these species are in general one step higher than for *A. fumigatus.*
3. The MIC values for isolates of *A. niger* and *A. versicolor* are in general higher than those for *A. fumigatus*. Whether this translates into a poorer clinical response is unknown.

IE = There is insufficient evidence (IE) to set breakpoints for these species.

Using CLSI methods, breakpoints for itraconazole have only been established for *Candida* species from superficial mycotic infections. The CLSI breakpoints are: susceptible ≦0.125 mg/L and resistant ≥1 mg/L.

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The *in vitro* susceptibility of fungi to itraconazole depends on the inoculum size, incubation temperature, growth phase of the fungi, and the culture medium used. For these reasons, the minimum inhibitory concentration of itraconazole may vary widely. Susceptibility in the table below is based on $MIC_{90}$ <1 mg itraconazole/L. There is no correlation between *in vitro* susceptibility and clinical efficacy.

| **Commonly susceptible species** |
|---|
| Aspergillus spp.[2] |
| *Blastomyces dermatitidis*[1] |
| *Candida albicans* |
| *Candida parapsilosis* |
| Cladosporium spp. |
| *Coccidioides immitis*[1] |
| *Cryptococcus neoformans* |
| *Epidermophyton floccosum* |
| Fonsecaea spp. [1] |
| Geotrichum spp. |
| Histoplasma spp. |
| Malassezia (formerly Pityrosporum*)* spp. |
| Microsporum spp. |
| *Paracoccidioides brasiliensis*[1] |
| *Penicillium marneffei*[1] |
| *Pseudallescheria boydii* |
| *Sporothrix schenckii* |
| Trichophyton spp. |
| Trichosporon spp. |
| **Species for which acquired resistance may be a problem** |
| *Candida glabrata*[3] |

| |
|---|
| *Candida krusei* |
| *Candida tropicalis*[3] |
| **Inherently resistant organisms** |
| Absidia spp. |
| Fusarium spp. |
| Mucor spp. |
| Rhizomucor spp. |
| Rhizopus spp. |
| *Scedosporium proliferans* |
| Scopulariopsis spp. |

[1] These organisms may be encountered in patients who have returned from travel outside Europe.
[2] Itraconazole-resistant strains of *Aspergillus fumigatus* have been reported.
[3] Natural intermediate susceptibility.

Paediatric Population

The tolerability and safety of itraconazole oral solution was studied in the prophylaxis of fungal infections in 103 neutropenic paediatric patients aged 0 to 14 years (median 5 years) in an open-label uncontrolled phase III clinical study. Most patients (78%) were undergoing allogenic bone marrow transplantation for haematological malignancies. All patients received 5-mg/kg/day of itraconazole oral solution as a single or divided dose. Due to the design of the study, no formal conclusion with regard to efficacy could be derived. The most common adverse events considered definitely or possibly related to itraconazole were vomiting, abnormal liver function, and abdominal pain.

## 5.2 Pharmacokinetic properties

*General pharmacokinetic characteristics*
Pharmacokinetic studies of itraconazole after single or repeated administration were performed in healthy volunteers, in certain population groups and in patients. In general, itraconazole is well absorbed. Maximum plasma levels are reached within 2-5 hours after oral intake. Itraconazole is subject to an extensive hepatic metabolism developing numerous metabolites thereby. Main metabolite is hydroxy-itraconazole, whose plasma concentrations reach the 2fold of unchanged active substance. The terminal half-life of itraconazole is 17 hours after single administration and increases to 34-42 hours in repeated administration. The pharmacokinetics of itraconazole are characterized by non-linearity. Consequently, the active substance accumulates in plasma after multiple administration. Steady state concentrations are achieved within 15 days with $C_{max}$ values reaching 0.5 microgram/ml after 100 mg itraconazole once daily, 1.1 micrograms/ml after 200 mg itraconazole once daily and 2.0 micrograms/ml after 200 mg twice daily. If treatment is terminated, the plasma concentrations of itraconazole fall almost below the detection limit within 7 days. Due to a

saturation mechanism during metabolization in the liver, the itraconazole clearance decreases at higher dosage. Itraconazole is excreted in the urine (approx. 35%) and with the faeces (approx. 54%) in the form of inactive metabolites.

*Absorption*
After oral intake, itraconazole is rapidly taken up by the organism. Maximum plasma levels of unchanged active substance are achieved within a period of 2-5 hours after intake. The absolute oral bioavailability of itraconazole is 55%. A maximum oral bioavailability is achieved if itraconazole is taken directly after a meal.

*Distribution*
Itraconazole is bound to plasma proteins at 99.8%, especially to plasma albumin (99.6% of the hydroxy metabolite). Itraconazole has also distinct affinity for lipids. Only 0.2% of the active substance is present in plasma in free form. Itraconazole has an apparent distribution volume of > 700 l in the body, which points to extensive distribution into body tissues: the concentrations identified in lung, kidney, liver, bone, stomach, spleen and muscles were twice to 3 times higher than the corresponding plasma concentrations. The brain-plasma quotient was about 1.
The itraconazole levels in the skin are up to 4 times higher than in plasma. The elimination from the skin depends on epidermal regeneration.

Therapeutic levels in the vaginal tissue remain for further 3 days after cessation of a 1-day therapy with 200 mg itraconazole twice daily. Therefore a 1-day therapy is sufficient.

*Biotransformation*
Itraconazole is extensively metabolised in the liver with a variety of metabolites developing thereby. Main metabolite is hydroxy-itraconazole, which has an antimycotic *in vitro* activity comparable to itraconazole. The plasma concentrations of the hydroxy metabolite are about twice as high as the itraconazole plasma concentrations.
As seen in *in vitro* studies, CYP 3A4 is an important enzyme involved in the metabolization of itraconazole.

*Elimination*
Itraconazole is excreted via urine in the form of inactive metabolites at approx. 35% via the urine and at approx. 54% with the faeces within one week. Renal excretion of the unchanged substance is less than 0.03% of a dose, whereas the excretion via the faeces varies between 3 and 18% of a dose.

Since the quantity of itraconazole passing from keratic tissues into the organism seems negligible, it can be assumed that itraconazole is eliminated from these tissues via dermal regeneration. Whereas itraconazole cannot be detected any more in plasma within 7 days after discontinuation of therapy, therapeutic levels in the skin are maintained over 2-4 weeks after a 4-week therapy. In the nail, itraconazole levels can

be identified already within 1 week after initiating therapy. After cessation of a 3-month therapy, therapeutic levels are still detectable for at least 6 months.

*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 (see sections 4.2 and 4.4).

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

*Paediatric Population*
Two pharmacokinetic studies have been conducted in neutropenic children aged 6 months to 14 years in which itraconazole oral solution was administered 5 mg/kg once or twice daily. The exposure to itraconazole was somewhat higher in older children (6 to 14 years) compared to younger children. In all children, effective plasma concentrations of itraconazole were reached within 3 to 5 days after initiation of treatment and maintained throughout treatment.

### 5.3 Preclinical safety data

Nonclinical data on itraconazole revealed no indications for gene toxicity, primary carcinogenicity or impairment of fertility. At high doses, effects were observed in the adrenal cortex, liver and the mononuclear phagocyte system but appear to have a low relevance for the proposed clinical use. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats and mice at high doses. 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

*Other Ingrediens*

sucrose

maize starch

Hypromellose

Macrogol

*Body*

Titanium dioxide (E171)

Gelatin

*Cap*

Titanium dioxide (E 171)

Gelatin

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Do not store above 30 °C.
Keep the blister in the outer carton in order to protect from light.

## 6.5 Nature and contents of container

The capsules are packed in blister strips. The blister strips are packed in a carton box

PVC/aluminium or PVC/PVDC/aluminium blister

4, 6, 7, 8, 14, 15, 18, 20, 28, 30, 60, 84, 90 and 100 capsules,

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused product or waste should be disposed of in accordance with local requirements

## 7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1303

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

23/12/2012

## 10 DATE OF REVISION OF THE TEXT

28/07/2013