

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Itrakonazol Actavis 100 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule, hard contains 100 mg of itraconazole.

Excipient with known effect: Each capsule, hard contains 244 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard

No. 0 hard gelatine capsules, opaque green cap and body, containing yellowish-beige spherical micro-granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Itraconazole is indicated for the treatment of the following fungal infections verified by direct microscopy and/or cultures where systemic treatment is considered necessary:
Vulvovaginal candidiasis, oral candidiasis, pityriasis versicolor, dermatomycoses, onychomycoses (caused by dermatophytes and yeasts).

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

4.2 Posology and method of administration

Posology

Adults:

Vulvovaginal candidiasis:

200 mg in the morning and 200 mg in the evening for 1 day.

Oral candidiasis:

100 mg once daily for 2 weeks.

Pityriasis versicolor:

200 mg once daily for 1 week.

Tinea corporis/cruris:

100 mg once daily for 2 weeks.

Tinea pedis/manus:

100 mg once daily for 4 weeks.

Onychomycoses:

Pulse treatment:

Toenails with or without infected fingernails:

200 mg twice daily for 7 days, followed by a treatment-free interval of 3 weeks, 3 times in total.

Fingernails:

200 mg twice daily for 7 days, followed by a treatment-free interval of 3 weeks, 2 times in total, provided that the fungal infection does not involve the entire nail plate and nail matrix in which case 3 pulse treatments should be given.

or:

200 mg once daily for 3 months.

For treatment of special patient groups such as elderly, patients with impaired immune systems, impaired liver or kidney function see section 4.4.

For skin infections optimal clinical effects are reached at 2-4 weeks after cessation of treatment and for nail infections at 6-9 months after the cessation of treatment. This is because elimination of itraconazole from skin and nails is slower than from plasma.

Paediatric population

Since clinical data on the use of itraconazole oral solution 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).

Elderly

Since clinical data on the use of itraconazole in elderly patients are limited, it is advised to use /.../ capsules in these patients only if the potential benefits outweigh the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see section 4.4).

Hepatic impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. (See sections 4.4 and 5.2).

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 drug is administered in this patient population and adjusting the dose may be considered.

Decreased gastric acidity

Absorption of itraconazole from itraconazole capsules may be impaired when gastric acidity is reduced. 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. H₂-antagonists, proton-pump inhibitors) it is advisable to administer itraconazole capsules with acid containing beverages.

Method of administration

/.../ capsules are for oral use.

The capsules should be taken immediately after meals.

The capsules should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 section 4.4).

Itraconazole Actavis should not be given to pregnant women except in life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus. See section 4.6.

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

Co-administration of itraconazole is contraindicated with a number of CYP3A4 substrates such as the examples listed below (see sections 4.4 and 4.5):

Analgesics; Anaesthetics		
Ergot alkaloids (e.g. dihydroergotamine, ergometrine, ergotamine, methylergometrine)		
Anti-bacterials for Systemic Use; Anti-mycobacterials; Antimycotics for Systemic Use		
Isavuconazole		
Anthelmintics; Antiprotozoals		
Halofantrine		
Antihistamines for Systemic Use		
Astemizole	Mizolastine	Terfenadine
Antineoplastic Agents		
Irinotecan	Venetoclax (in patients with chronic lymphocytic leukaemia during initiation and dose titration phase of venetoclax)	
Antithrombotic Agents		
Dabigatran	Ticagrelor	
Antivirals for Systemic Use		
Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir)		
Cardiovascular System (Agents Acting on the Renin-Angiotensin System; Antihypertensives; Beta Blocking Agents; Calcium Channel Blockers; Cardiac Therapy; Diuretics)		
Aliskiren	Eplerenone	Quinidine
Bepidil	Finerenone	Ranolazine
Disopyramide	Ivabradine	Sildenafil (pulmonary hypertension)
Dofetilide	Lercanidipine	

Dronedarone	Nisoldipine	
Gastrointestinal Drugs, including Antidiarrheals, Intestinal Anti-inflammatory/Anti-infective Agents; Antiemetics and Antinauseants; Drugs for Constipation; Drugs for Functional Gastrointestinal Disorders		
Cisapride	Domperidone	Naloxegol
Immunosuppressants		
Voclosporin		
Lipid Modifying Agents		
Lovastatin	Lomitapide	Simvastatin
Psychoanaleptics; Psycholeptics (e.g., antipsychotics, anxiolytics, and hypnotics)		
Lurasidone	Pimozide	Sertindole
Midazolam (oral)	Quetiapine	Triazolam
Urologicals		
Avanafil	Darifenacin	Solifenacin (in patients with severe renal impairment or moderate to severe hepatic impairment)
Dapoxetine	Fesoterodine (in patients with moderate or severe renal or hepatic impairment).	Vardenafil (in patients older than 75 years).
Miscellaneous Drugs and Other Substances		
Colchicine (in patients with renal or hepatic impairment)	Eliglustat (in patients that are CYP2D6 poor metabolisers (PM), CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) that are taking a strong or moderate CYP2D6 inhibitor).	

An elevated plasma level of these drugs due to concomitant administration of itraconazole may increase or prolong both therapeutic effects and side effects to such an extent that a potentially serious situation may arise. For example, elevated plasma levels of some of these drugs may lead to QT prolongation and ventricular arrhythmias, including cases of torsade de pointes, a potentially fatal arrhythmia.

Specific examples are listed in section 4.5.

4.4 Special warnings and precautions for use

Cross-hypersensitivity

There is no information regarding cross-hypersensitivity between itraconazole and other antimycotic azoles. Caution should be used in prescribing /.../ capsules to patients hypersensitive to other azoles.

Cardiac effects

In a healthy volunteer study of intravenous itraconazole, transient, asymptomatic decreases in left ventricular ejection fraction were 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. The individual risk-benefit assessment should consider factors such as the severity of the indication, the dosing regimen (e.g. total daily dose), the duration of treatment 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. Patients with these risk factors should be informed of the signs and symptoms of congestive heart failure. During treatment caution should be exercised and the patient monitored for the signs and symptoms of congestive heart failure. Itraconazole should be discontinued if such signs or symptoms occur during treatment.

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 due to an increased risk of CHF (see section 4.5).

Hepatic effects

Very rare cases of severe hepatotoxicity, including some cases of fatal acute liver failure, have been reported in patients treated with itraconazole. Some of these cases involved patients who had 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. Patients should be instructed to promptly report to their physician any 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. Most cases of severe 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 an active liver disease, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit outweighs the risk of hepatic injury. In such cases, liver enzyme monitoring is necessary.

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 1 hour before and at least 2 hours after the intake of itraconazole capsules. In patients with impaired gastric acidity, whether resulting from a medical condition (e.g. achlorhydria) or a concomitant medication (e.g. patients taking medicines that reduce gastric acidity), it is advisable to administer itraconazole with acid drink, such as a non-diet cola beverage, since adequate absorption requires a low pH in the stomach.

The serum level of itraconazole should be monitored and the dose of itraconazole increased as needed (see sections 4.5 and 5.2).

Paediatric population

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

Elderly

Clinical data on the use of itraconazole in elderly patients is limited. Itraconazole should not be used in these patients unless the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic impairment

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 (see section 5.2).

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 drugs, 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).

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 (see section 5.2). 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 4.3 and 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 and non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Cystic fibrosis

In cystic fibrosis patients, variability in plasma levels of itraconazole leading to subtherapeutic concentrations has been observed. The risk for subtherapeutic concentrations may be higher in < 16 year olds. If a patient does not respond to itraconazole capsules, consideration should be given to switching to alternative therapy.

Neuropathy

If neuropathy occurs which may be attributable to itraconazole, 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 drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given.

Interaction potential

Co-administration of specific medicinal products with itraconazole may result in changes in the efficacy or safety of itraconazole and/or the co-administered medicinal product, life-threatening effects and/or sudden death. Medicinal products contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in section 4.3 Contraindications and section 4.5 Interactions with other medicinal products and other interactions.

Excipient(s)

Sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 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. Itraconazole is a strong CYP3A4 inhibitor and, a P-glycoprotein inhibitor and Breast Cancer Resistance Protein (BCRP) inhibitor.

Itraconazole may modify the pharmacokinetics of other substances that share this metabolic or these protein transporter pathways.

Examples of drugs that may impact on the plasma concentration of itraconazole are presented by drug class in Table 1 below. Examples of drugs that may have their plasma concentrations impacted by itraconazole are presented in Table 2 below. Due to the number of interactions, the potential changes in safety or efficacy of the interacting drugs are not included. The list of examples of interacting drugs in the tables below is not comprehensive and therefore the product information of each drug that is co-administered with itraconazole should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

The interactions described in these tables are categorised as contraindicated, not recommended or to be used with caution with itraconazole taking into account the extent of the concentration increase and the safety profile of the interacting drug (see also sections 4.3 and 4.4 for further information). The interaction potential of the listed drugs was evaluated based on human pharmacokinetic studies with itraconazole, and/or human pharmacokinetic studies with other strong CYP3A4 inhibitors (e.g. ketoconazole) and/or in vitro data:

- ‘Contraindicated’: Under no circumstances is the drug to be co-administered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.
- ‘Not recommended’: The use of the drug 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 co-administration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the concomitantly administered drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations of the co-administered drug be measured.
- ‘Use with caution’: Careful monitoring is recommended when the drug is co-administered with itraconazole. Upon co-administration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations of the co-administered drug be measured.

The interactions listed in these tables have been characterised in studies that were performed with recommended doses of itraconazole. However, the extent of interaction may be dependent on the dose of itraconazole administered. A stronger interaction may occur at a higher dose or with a shorter dosing interval. Extrapolation of the findings with other dosing scenarios or different drugs should be done with caution.

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 drugs whose metabolism is affected by itraconazole. (see section 5.2)

Table 1: Examples of drugs that may impact the plasma concentration of itraconazole, presented by drug class

Examples of medicinal products (Per Orale [PO] Single Dose unless otherwise stated) within class	Expected/Potential effect on itraconazole levels (↑ = increase; ↔ = no change; ↓ = decrease)	Clinical comment (see above for additional information and also sections 4.3 and 4.4)
Anti-bacterials for Systemic Use; Anti-mycobacterials		
Isoniazid	Although not studied directly, isoniazid is likely to decrease the concentrations of itraconazole.	Not recommended
Rifampicin PO 600 mg OD	Itraconazole AUC ↓	Not recommended
Rifabutin PO 300 mg OD	Itraconazole C _{max} ↓ 71%, AUC ↓ 74%	Not recommended
Ciprofloxacin PO 500 mg BID	Itraconazole C _{max} ↑ 53%, AUC ↑ 82%	Use with caution
Erythromycin 1 g	Itraconazole C _{max} ↑ 44%, AUC ↑ 36%	Use with caution
Clarithromycin PO 500 mg BID	Itraconazole C _{max} ↑ 90%, AUC ↑ 92%	Use with caution
Antiepileptics		
Carbamazepine, Phenobarbital	Although not studied directly, these drugs are likely to decrease concentrations of itraconazole.	Not recommended
Phenytoin PO 300 mg OD	Itraconazole C _{max} ↓ 83%, AUC ↓ 93% Hydroxyitraconazole C _{max} ↓ 84%, AUC ↓ 95%	Not recommended
Antineoplastics Agents		
Idelalisib	Although not studied directly, idelalisib is likely to increase the concentrations of itraconazole.	Use with caution
Antivirals for Systemic Use		
Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir)	Although not studied directly, these drugs are expected to increase the concentrations of itraconazole.	Contraindicated
Efavirenz 600 mg	Itraconazole C _{max} ↓ 37%, AUC ↓ 39%; Hydroxyitraconazole C _{max} ↓ 35%, AUC ↓ 37%	Not recommended
Nevirapine PO 200 mg OD	Itraconazole C _{max} ↓ 38%, AUC ↓ 62%	Not recommended
Cobicistat, Darunavir (boosted), Elvitegravir (ritonavir-boosted), Fosamprenavir (ritonavir-boosted), Ritonavir, Saquinavir (ritonavir-boosted)	Although not studied directly, these drugs are expected to increase the concentrations of itraconazole.	Use with caution
Indinavir PO 800 mg TID	Itraconazole concentration ↑	Use with caution
Calcium Channel Blockers		

Diltiazem	Although not studied directly, diltiazem is likely to increase the concentration of itraconazole.	Use with caution
Drugs for Acid Related Disorders		
Antacids (aluminium, calcium, magnesium, or sodium bicarbonate), H ₂ -receptor antagonists (e.g., cimetidine, ranitidine), Proton pump inhibitors (e.g., lansoprazole, omeprazole, rabeprazole)	Itraconazole C _{max} ↓, AUC ↓	Use with caution
Respiratory System: Other Respiratory System Products		
Lumacaftor/Ivacaftor PO 200/250 mg BID	Itraconazole concentration ↓	Not recommended
Miscellaneous		
St. John's Wort (<i>Hypericum perforatum</i>)	Although not studied directly, St. John's Wort is likely to decrease the concentration of itraconazole.	Not recommended

Table 2 Examples of drugs that may have their plasma concentrations impacted by itraconazole, presented by drug class

Examples of medicinal products (PO Single Dose unless otherwise stated) within class	Expected/Potential effect on drug levels (↑ = increase; ↔ = no change; ↓ = decrease)	Clinical comment (see above for additional information and also sections 4.3 and 4.4)
Analgesics; Anaesthetics		
Ergot alkaloids (e.g., dihydroergotamine, ergometrine, ergotamine, methylethergometrine)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Eletriptan, Fentanyl	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Alfentanil, Buprenorphine (IV and sublingual), Cannabinoids, Methadone, Sufentanil	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Oxycodone PO 10 mg	Oxycodone PO: C _{max} ↑ 45%, AUC ↑ 2.4-fold	Use with caution
Oxycodone IV 0.1 mg/kg	Oxycodone IV: AUC ↑ 51%	Use with caution
Anti-bacterials for Systemic Use; Anti-mycobacterials; Antimycotics for Systemic Use		
Isavuconazole	Although not studied directly, itraconazole is likely to increase the concentrations of isavuconazole.	Contraindicated
Bedaquiline	Although not studied directly, itraconazole is likely to increase the concentrations of bedaquiline.	Not recommended
Rifabutin PO 300 mg OD	Rifabutin concentration ↑ (extent unknown)	Not recommended
Clarithromycin PO 500 mg BID	Clarithromycin concentration ↑	Use with caution

Delamanid	Although not studied directly, itraconazole is likely to increase the concentrations of delamanid.	Use with caution
Antiepileptics		
Carbamazepine	Although not studied directly, itraconazole is likely to increase the concentrations of carbamazepine.	Not recommended
Anti-inflammatory and Antirheumatic Products		
Meloxicam 15 mg	Meloxicam $C_{\max}$ ↓ 64%, AUC ↓ 37%	Use with caution
Anthelmintics; Antiprotozoals		
Halofantrine	Although not studied directly, itraconazole is likely to increase the concentrations of halofantrine.	Contraindicated
Artemether-lumefantrine, Praziquantel	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Quinine 300 mg	Quinine $C_{\max}$ ↔, AUC ↑ 96%	Use with caution
Antihistamines for Systemic Use		
Astemizole, Mizolastine, Terfenadine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Ebastine 20 mg	Ebastine $C_{\max}$ ↑ 2.5-fold, AUC ↑ 6.2-fold Carebastine $C_{\max}$ ↔, AUC ↑ 3.1-fold	Not recommended
Bilastine, Rupatadine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Antineoplastic Agents		
Irinotecan	Although not studied directly, itraconazole is likely to increase the concentrations of irinotecan and its active metabolite.	Contraindicated
Venetoclax	Although not studied directly, itraconazole is likely to increase the concentrations of venetoclax.	Contraindicated in patients with chronic lymphocytic leukaemia during initiation and dose titration phase of venetoclax. Otherwise, not recommended unless the benefits outweigh the risks. Refer to the venetoclax prescribing information.
Axitinib, Bosutinib, Cabazitaxel, Cabozantinib, Ceritinib, Crizotinib, Dabrafenib, Dasatinib, Docetaxel, Everolimus, Glasdegib, Ibrutinib, Lapatinib, Nilotinib, Pazopanib, Regorafenib, Sunitinib, Temsirolimus, Trabectedin, Trastuzumab emtansine, Vinca alkaloids (e.g., vinflunine,	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs except for cabazitaxel and regorafenib. No statistically significant change in cabazitaxel exposure, but a high variability in the results was observed. Regorafenib AUC is expected to decrease (by estimation of active moiety).	Not recommended

vinorelbine)		
Cobimetinib 10 mg	Cobimetinib C _{max} ↑ 3.2-fold, AUC ↑ 6.7-fold	Not recommended
Entrectinib	Entrectinib C _{max} ↑ 73%, AUC ↑ 6.0-fold	Not recommended
Olaparib 100 mg	Olaparib C _{max} ↑ 40%, AUC ↑ 2.7-fold	Not recommended
Talazoparib	Talazoparib C _{max} ↑ 40%, AUC ↑ 56%	Not recommended
Alitreteinoin (oral), Bortezomib, Brentuximab vedotin, Erlotinib, Idelalisib, Imatinib, Nintedanib, Panobinostat, Ponatinib, Ruxolitinib, Sonidegib, Tretinoin (oral)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs	Use with caution
Busulfan 1 mg/kg Q6h	Busulfan C _{max} ↑, AUC ↑	Use with caution
Gefitinib 250 mg	Gefitinib 250 mg C _{max} ↑, AUC ↑ 78%	Use with caution
Pemigatinib	Pemigatinib C _{max} ↑ 17%, AUC ↑ 91%	Use with caution
Antithrombotic Agents		
Dabigatran, Ticagrelor	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Apixaban, Edoxaban, Rivaroxaban, Vorapaxar	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Cilostazol, Coumarins (e.g., warfarin)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs	Use with caution
Antivirals for Systemic Use		
Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir)	Itraconazole may increase paritaprevir concentrations.	Contraindicated
Elbasvir/Grazoprevir, Tenofovir alafenamide fumarate (TAF), Tenofovir disoproxil fumarate (TDF)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Cobicistat, Elvitegravir (ritonavir-boosted), Glecaprevir/Pibrentasvir, Maraviroc, Ritonavir, Saquinavir	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution

Indinavir PO 800 mg TID	Indinavir C _{max} ↔, AUC ↑	Use with caution
Cardiovascular System (Agents Acting on the Renin-Angiotensin System; Antihypertensives; Beta Blocking Agents; Calcium Channel Blockers; Cardiac Therapy; Diuretics)		
Bepridil, Disopyramide, Dofetilide, Dronedaron, Eplerenone, Finerenone, Ivabradine, Lercanidipine, Nisoldipine, Ranolazine, Sildenafil (pulmonary hypertension)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Aliskiren 150 mg	Aliskiren C _{max} ↑ 5.8-fold, AUC ↑ 6.5-fold	Contraindicated
Quinidine 100 mg	Quinidine C _{max} ↑ 59%, AUC ↑ 2.4-fold	Contraindicated
Felodipine 5 mg	Felodipine C _{max} ↑ 7.8-fold, AUC ↑ 6.3-fold	Not recommended
Riociguat, Tadalafil (pulmonary hypertension)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Bosentan, Diltiazem, Guanfacine, Other Dihydropyridines (e.g., amlodipine, isradipine, nifedipine, nimodipine), Verapamil	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Digoxin 0.5 mg	Digoxin C _{max} ↑ 34%, AUC ↑ 68%	Use with caution
Nadolol 30 mg	Nadolol C _{max} ↑ 4.7-fold, AUC ↑ 2.2-fold	Use with caution
Corticosteroids for Systemic Use; Drugs for Obstructive Airway Diseases		
Ciclesonide, Salmeterol	Although not studied directly, itraconazole is likely to increase the concentrations of salmeterol and the active metabolite of ciclesonide.	Not recommended
Budesonide INH 1 mg SD	Budesonide INH C _{max} ↑ 65%, AUC ↑ 4.2-fold; Budesonide (other formulations) concentration ↑	Use with caution
Dexamethasone IV 5 mg Dexamethasone PO 4.5 mg	Dexamethasone IV: C _{max} ↔, AUC ↑ 3.3-fold Dexamethasone PO: C _{max} ↑ 69%, AUC ↑ 3.7-fold	Use with caution
Fluticasone INH 1 mg BID	Fluticasone INH concentration ↑	Use with caution
Methylprednisolone 16 mg	Methylprednisolone PO C _{max} ↑ 92%, AUC ↑ 3.9-fold Methylprednisolone IV AUC ↑ 2.6-fold	Use with caution
Fluticasone nasal	Although not studied directly, itraconazole is likely to increase the concentrations of nasally-administered fluticasone.	Use with caution
Drugs Used in Diabetes		
Repaglinide 0.25 mg	Repaglinide C _{max} ↑ 47%, AUC ↑ 41%	Use with caution
Saxagliptin	Although not studied directly, itraconazole is likely to increase the concentrations of saxagliptin.	Use with caution

Gastrointestinal Drugs, including Antidiarrheals, Intestinal Anti-inflammatory/Anti-infective Agents; Antiemetics and Antinauseants; Drugs for Constipation; Drugs for Functional Gastrointestinal Disorders		
Cisapride, Naloxegol	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Domperidone 20 mg	Domperidone C_{max} ↑ 2.7-fold, AUC ↑ 3.2-fold	Contraindicated
Aprepitant, Loperamide, Netupitant	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Immunosuppressants		
Voclosporin	Although not studied directly, itraconazole is likely to increase the concentrations of voclosporin.	Contraindicated
Sirolimus (rapamycin)	Although not studied directly, itraconazole is likely to increase the concentrations of sirolimus.	Not recommended
Cyclosporine, Tacrolimus	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Tacrolimus IV 0.03 mg/kg OD	Tacrolimus IV concentration ↑	Use with caution
Lipid Modifying Agents		
Lomitapide	Although not studied directly, itraconazole is likely to increase the concentrations of lomitapide.	Contraindicated
Lovastatin 40 mg,	Lovastatin C_{max} ↑ 14.5->20-fold, AUC ↑ >14.8 - >20-fold Lovastatin acid C_{max} ↑ 11.5-13-fold, AUC ↑ 15.4-20-fold	Contraindicated
Simvastatin 40 mg	Simvastatin acid C_{max} ↑ 17-fold, AUC ↑ 19-fold	Contraindicated
Atorvastatin	Atorvastatin acid: C_{max} ↔ to ↑2.5-fold, AUC ↑ 40% to 3-fold	Not recommended
Psychoanaleptics; Psycholeptics (e.g., antipsychotics, anxiolytics, and hypnotics)		
Lurasidone, Pimozide, Quetiapine, Sertindole	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Midazolam (oral) 7.5 mg	Midazolam (oral) C_{max} ↑ 2.5 to 3.4-fold, AUC ↑ 6.6 to 10.8-fold	Contraindicated
Triazolam 0.25 mg	Triazolam C_{max} ↑, AUC ↑	Contraindicated
Alprazolam 0.8 mg	Alprazolam C_{max} ↔, AUC ↑ 2.8-fold	Use with caution
Aripiprazole 3 mg	Aripiprazole C_{max} ↑ 19%, AUC ↑ 48%	Use with caution
Brotizolam 0.5 mg	Brotizolam C_{max} ↔, AUC ↑ 2.6-fold	Use with caution
Buspirone 10 mg	Buspirone C_{max} ↑ 13.4-fold, AUC ↑ 19.2-fold	Use with caution
Midazolam (iv) 7.5 mg	Midazolam (iv) 7.5 mg: concentration ↑; Although not studied directly, itraconazole is likely to increase the concentrations of midazolam following oromucosal administration.	Use with caution

Risperidone 2-8 mg/day	Risperidone and active metabolite concentration ↑	Use with caution
Zopiclone 7.5 mg	Zopiclone C _{max} ↑ 30%, AUC ↑ 70%	Use with caution
Cariprazine, Galantamine, Haloperidol, Reboxetine, Venlafaxine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Respiratory System: Other Respiratory System Products		
Lumacaftor/Ivacaftor PO 200/250 mg BID	Ivacaftor C _{max} ↑ 3.6-fold, AUC ↑ 4.3-fold Lumacaftor C _{max} ↔, AUC ↔	Not recommended
Ivacaftor	Although not studied directly, itraconazole is likely to increase the concentrations of ivacaftor.	Use with caution
Sex Hormones and Modulators of the Genital System; Other Gynaecologicals		
Cabergoline, Dienogest, Ulipristal	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Urologicals		
Avanafil, Dapoxetine, Darifenacin	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Fesoterodine	Although not studied directly, itraconazole is likely to increase the concentrations of the active metabolites, 5-hydroxymethyl tolterodine.	Moderate or severe renal or hepatic impairment: Contraindicated Mild renal or hepatic impairment: Concomitant use should be avoided Normal renal or hepatic function: Use with caution with a maximum fesoterodine dose of 4 mg.
Solifenacin	Although not studied directly, itraconazole is likely to increase the concentrations of solifenacin.	Severe renal impairment: Contraindicated Moderate or severe hepatic impairment: Contraindicated Use with caution in all other patients with a maximum solifenacin dose of 5 mg.
Vardenafil	Although not studied directly, itraconazole is likely to increase the concentrations of vardenafil.	Contraindicated in patients older than 75 years; otherwise not recommended.
Alfuzosin, Silodosin, Tadalafil (erectile dysfunction and benign prostatic hyperplasia), Tamsulosin, Tolterodine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Dutasteride, Imidafenacin, Sildenafil (erectile dysfunction)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution

Oxybutynin 5 mg	Oxybutynin C_{max} ↑ 2-fold, AUC ↑ 2-fold N-desethyloxybutynin C_{max} ↔, AUC ↔ Following transdermal administration: Although not studied directly, itraconazole is likely to increase the concentrations of oxybutynin following transdermal administration.	Use with caution
Miscellaneous Drugs and Other Substances		
Colchicine	Although not studied directly, itraconazole is likely to increase the concentrations of colchicine	Contraindicated in patients with renal or hepatic impairment. Not recommended in other patients.
Eliglustat	Although not directly studied, itraconazole is expected to increase the concentrations of eliglustat.	Contraindicated in CYP2D6 poor metabolisers (PM). Contraindicated in CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) taking a strong or moderate CYP2D6 inhibitor. Use with caution in CYP2D6 IMs and EMs. In CYP2D6 EMs with mild hepatic impairment, an eliglustat dose of 84mg/day should be considered.
Cinacalcet	Although not studied directly, itraconazole is likely to increase the concentrations of cinacalcet.	Use with caution

OD = once daily

BID = twice daily

TID = three times daily

SD = single dose

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 first menstrual period following the end of itraconazole therapy.

Pregnancy

/.../ capsules must not be given pregnant women except in 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). When administered at high doses to pregnant rats (40 mg/kg/day or higher) and mice (80 mg/kg/day or higher), itraconazole has been shown to increase the incidence of foetal abnormalities and to produce adverse effects on the embryo. Itraconazole has been shown to cross the placenta in a rat model.

There is limited clinical 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.

Breast-feeding

Very small amounts of itraconazole are excreted in human milk. The expected benefits of treatment with /.../ capsules should therefore be weighed against the potential risk of breast-feeding. In case of doubt the patient should not breast-feed.

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 (Special warnings and precautions for use) 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 for the treatment of dermatomycoses or onychomycoses, and from spontaneous reporting.

The table below presents adverse drug reactions by System Organ Class. Within each System Organ Class, the adverse drug reactions are presented by incidence, using the following convention: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data).

Adverse Drug Reactions	
Infections and infestations	
<i>Uncommon</i>	Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and lymphatic system disorders	
<i>Rare</i>	Leukopenia
Immune system disorders	
<i>Uncommon</i>	Hypersensitivity*
<i>Rare</i>	Serum sickness, Angioneurotic oedema, Anaphylactic reaction

Endocrine disorders	
<i>Not known</i>	Pseudoaldosteronism
Metabolism and nutrition disorders	
<i>Rare</i>	Hypertriglyceridaemia
Nervous system disorders	
<i>Common</i>	Headache
<i>Rare</i>	Tremor, Paraesthesia, Hypoaesthesia, Dysgeusia
Eye disorders	
<i>Rare</i>	Visual disturbances (including blurred vision and diplopia)
Ear and labyrinth disorders	
<i>Rare</i>	Transient or permanent hearing loss*, Tinnitus
Cardiac disorders	
<i>Rare</i>	Congestive heart failure*
Respiratory, thoracic and mediastinal disorders	
<i>Rare</i>	Dyspnoea
Gastrointestinal disorders	
<i>Common</i>	Abdominal pain, Nausea
<i>Uncommon</i>	Diarrhoea, Vomiting, Constipation, Dyspepsia, Flatulence
<i>Rare</i>	Pancreatitis
Hepatobiliary disorders	
<i>Uncommon</i>	Hepatic function abnormal
<i>Rare</i>	Serious hepatotoxicity (including some cases of fatal acute liver failure)*, Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
<i>Uncommon</i>	Urticaria, Rash, Pruritus
<i>Rare</i>	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Renal and urinary disorders	
<i>Rare</i>	Pollakiuria
Reproductive system and breast disorders	
<i>Uncommon</i>	Menstrual disorders
<i>Rare</i>	Erectile dysfunction
General disorders and administration site conditions	
<i>Rare</i>	Oedema
Investigations	
<i>Rare</i>	Blood creatine phosphokinase increased

* see section 4.4.

Description of selected adverse reactions

The following is a list of additional ADRs associated with itraconazole that have been reported in clinical trials of itraconazole oral solution and itraconazole solution for infusion, 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 (see section 4.4), Dizziness, Somnolence

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

Itraconazole capsules

The safety of itraconazole capsules was evaluated in 165 paediatric patients aged 1 to 17 years who participated in 14 clinical trials (4 double-blind, placebo-controlled trials, 9 open-label trials and 1 trial had an open-label phase followed by a double-blind phase). These patients received at least one dose of itraconazole capsules for the treatment of fungal infections and provided safety data.

Based on pooled safety data from these clinical trials, the commonly reported adverse drug reactions (ADRs) in paediatric patients were Headache (3.0%), Vomiting (3.0%), Abdominal pain (2.4%), Diarrhoea (2.4%), Hepatic function abnormal (1.2%), Hypotension (1.2%), Nausea (1.2%), and Urticaria (1.2%). In general, the nature of ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric patients.

Itraconazole oral solution

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 10 mg/ml 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 national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms

In general, the symptoms of an overdose have been consistent with the adverse drug reactions (see section 4.8).

Treatment

In the event of an overdose, supportive measures should be employed. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

It is advisable to contact a poison control centre to obtain the latest recommendations for the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole and tetrazole derivatives
ATC-code: J02AC02

Mechanism of action

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

PK/PD relationship

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

Mechanism(s) 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- α -demethylase (the target enzyme)
- Point mutations in *ERG11* that lead to decreased affinity of 14- α -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 drugs has been observed within *Candida* species though resistance to one member of the class does not necessarily confer resistance to other azoles.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for itraconazole and are listed here: <https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx>

Interpretive breakpoints for itraconazole have not been established for *Candida* species and filamentous fungi, using Clinical and Laboratory Standards Institute (CLSI) methods, M60 Performance Standards Antifungal Susceptibility Testing of Yeasts. 2 nd edition, 2020.

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 (MIC) of itraconazole may vary widely. Susceptibility in the table below is based on MIC₉₀ < 1 mg itraconazole/L. There is no correlation between in vitro susceptibility and clinical efficacy.

Commonly susceptible species
<i>Aspergillus</i> spp. ²
<i>Blastomyces dermatitidis</i> ¹
<i>Candida albicans</i>
<i>Candida parapsilosis</i>
<i>Cladosporium</i> spp.
<i>Coccidioides immitis</i> ¹
<i>Cryptococcus neoformans</i>
<i>Epidermophyton floccosum</i>
<i>Fonsecaea</i> spp. ¹
<i>Geotrichum</i> spp.
<i>Histoplasma</i> spp.
<i>Malassezia</i> (formerly <i>Pityrosporum</i>) spp.
<i>Microsporum</i> spp.
<i>Paracoccidioides brasiliensis</i> ¹
<i>Talaromyces</i> (formerly <i>Penicillium</i>) <i>marneffei</i> ¹
<i>Pseudallescheria boydii</i>
<i>Sporothrix schenckii</i>
<i>Trichophyton</i> spp.
<i>Trichosporon</i> spp.
Species for which acquired resistance may be a problem
<i>Candida glabrata</i> ³
<i>Candida krusei</i>
<i>Candida tropicalis</i> ³
Inherently resistant organisms
<i>Absidia</i> spp.
<i>Fusarium</i> spp.
<i>Mucor</i> spp.
<i>Rhizomucor</i> spp.
<i>Rhizopus</i> spp.
<i>Scedosporium proliferans</i>
<i>Scopulariopsis</i> 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 allogeneic 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:

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. 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 $C_{\max}$ values of 0.5 µg/ml, 1.1 µg/ml and 2.0 µg/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. 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. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Absorption:

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration of the capsule. The observed absolute oral bioavailability of itraconazole is about 55% for an oral solution. Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given. (See section 4.4). Oral bioavailability is maximal when the capsules are taken immediately after a full meal. Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H₂-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see section 4.4 and section 4.5). Absorption of itraconazole under fasted conditions in these subjects is increased when itraconazole capsules are administered with an acidic beverage (such as a non-diet cola). When itraconazole capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H₂-receptor antagonist, itraconazole absorption was comparable to that observed when itraconazole capsules were administered alone. (See section 4.5.)

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 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, and the uptake into keratinous tissues, skin in particular, is up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

Metabolism:

Itraconazole is extensively metabolised by the liver into a large number of metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole which has in vitro antifungal activity comparable to itraconazole; trough plasma concentrations of this metabolite are about twice those of itraconazole.

Elimination:

Itraconazole is excreted mainly as inactive metabolites in urine (35%) and faeces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, faecal excretion of unchanged drug ranges from 3 to 18% of the dose.

As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeks after discontinuation of a 4- week treatment and in nail keratin – where itraconazole can be detected as early as 1 week after start of treatment – for at least six months after the end of a 3-month treatment period.

Special Populations

Hepatic impairment

Itraconazole is predominantly metabolised in the liver. A pharmacokinetic study was conducted in 6 healthy and 12 cirrhotic subjects who were administered a single 100-mg dose of itraconazole as a capsule. A statistically significant reduction in mean $C_{\max}$ (47%) and a twofold increase in the elimination half-life (37 ± 17 hours vs. 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC was similar in cirrhotic patients and in healthy subjects. Data are not available in cirrhotic patients during long-term use of itraconazole. (See sections 4.2 and 4.4.)

Renal impairment

Limited data are available on the use of oral itraconazole in patients with renal impairment. A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: $n=7$; hemodialysis: $n=7$; and continuous ambulatory peritoneal dialysis: $n=5$). In uremic subjects with a mean creatinine clearance of $13 \text{ ml/min.} \times 1.73 \text{ m}^2$, the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole ($T_{\max}$, $C_{\max}$, and $\text{AUC}_{0-8\text{h}}$). Plasma concentration-versus- time profiles showed wide intersubject variation in all three groups.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as $\text{CrCl } 50\text{--}79 \text{ ml/min}$), moderate (defined in this study as $\text{CrCl } 20\text{--}49 \text{ ml/min}$), and severe renal impairment (defined in this study as $\text{CrCl } <20 \text{ ml/min}$) were similar to that in healthy subjects, (range of means 42–49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively.) Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole. (See also section 4.2 and 4.4).

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

Itraconazole is not a primary carcinogen in rats up to 13 mg/kg/day (males) and 52 mg/kg/day (females), or in mice up to 80 mg/kg/day (1-fold of MRHD based on $\text{mg/m}^2/\text{day}$).

Nonclinical data on itraconazole revealed no indications for gene toxicity, primary carcinogenicity or impairment of fertility. At high doses, of 40 and 80 mg/kg/day in rats (1- and 2-fold of MRHD based on $\text{mg/m}^2/\text{day}$), 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.

A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, (no toxicity was observed up to 20 mg/kg/day (2-fold of MRHD based on $\text{mg/m}^2/\text{day}$), and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

Reproductive toxicology

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats from 40 mg/kg/day (1-fold of MRHD based on mg/m²/day) and mice from 80 mg/kg/day (1-fold of MRHD based on mg/m²/day). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and macroglossia. No teratogenic effects were found in rabbits up to 80 mg/kg/day dose (4-fold of MRHD based on mg/m²/day).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres (sucrose and maize starch), poloxamer and hypromellose.

Capsule shell: Gelatin and colouring agents (indigo carmine (E 132), quinoline yellow (E 104) and titanium dioxide (E 171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Aluminium/Aluminium blisters: either 4, 6, 15, 18, 28, 30 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2005-07-01/2010-07-01

10. DATE OF REVISION OF THE TEXT

2025-07-01