SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Itraconazole 10 mg/ml concentrate and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the Itraconazole concentrate contains 10 mg itraconazole.

One ampoule with 25 ml contains 250 mg itraconazole (itraconazole trihydrochloride salt formed *in situ*).

Each ml of the admixed solution contains 3.33 mg itraconazole.

One single dose of 200 mg itraconazole corresponds to 60 ml of the admixed solution.

Excipient(s) with known effect

One dose contains approximately 177 mg (7.7 mmol) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate and solvent for solution for infusion.

Itraconazole 10 mg/ml concentrate and solvent for solution for infusion is presented in a procedure pack consisting of:

a) 25 ml of Itraconazole 10 mg/ml concentrate for infusion, a clear, colourless or faintly yellow coloured solution presented in a glass ampoule.

b) 50 ml of Sodium Chloride 0.9 % w/v solvent for solution for infusion, a clear colourless solution presented in a polypropylene bag.

c) Extension line with 2-way stopcock and in-line filter.

Solvent for solution for infusion: Electrolytes (mEq /litre): sodium 154 mEq, chloride 154 mEq. 308 mOsmol/litre. pH 6.0 (4.0-7.0).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Itraconazole is indicated for the treatment of histoplasmosis.

Itraconazole is indicated in the following systemic fungal conditions when first-line systemic anti-fungal therapy is inappropriate or has proved ineffective. (This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity).

Treatment of aspergillosis, candidosis and cryptococcosis (including cryptococcal meningitis): in immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system.

Consideration should be given to national and/or local guidance regarding the appropriate use of antifungal agents.

4.2 Posology and method of administration

Posology

Itraconazole is given on the first two days in a loading dose twice daily, followed by once daily dosing.

Day 1 and 2 of the treatment: 1-hour infusion of 200 mg (60 ml of the admixed solution) Itraconazole twice daily (see section 6.6).

From day 3 on: one 1-hour infusion of 200 mg (60 ml of the admixed solution) Itraconazole each day. Safety for periods longer than 14 days has not been established.

Paediatric population

Clinical data on the use of itraconazole IV in paediatric patients are limited. The use of itraconazole IV in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks (see section 4.4).

Elderly

Since clinical data of the use of itraconazole in elderly patients are limited, it is advised to use itraconazole in these patients only if 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 (see section 4.4).

Renal impairment

Limited data are available on the use of intravenous itraconazole in patients with renal impairment.

Hydroxypropyl-β-cyclodextrin, a required component of itraconazole intravenous formulation, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment defined as creatinine clearance below 30 ml/min the use of itraconazole IV is contraindicated (see section 4.3).

In patients with mild and moderate renal impairment, itraconazole IV should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to the oral capsule formulation (see sections 4.4. and 5.2).

Hepatic impairment

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

Method of administration

Intravenous use.

This product is supplied with an extension line with a 2-way stopcock and 0.2 μm in-line filter. The dedicated extension line including the in-line filter must be used to ensure the correct administration of the product (see section 6.6).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Itraconazole cannot be used when administration of Sodium Chloride injection is contraindicated.

The excipient hydroxypropyl-β-cyclodextrin is eliminated through glomerular filtration. Therefore, Itraconazole is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 ml/min) see sections 4.4 and 5.2).

Co-administration of a number of CYP3A4 substrates is contraindicated with itraconazole IV (see sections 4.4 and 4.5).

Itraconazole must not be used during pregnancy for non life-threatening indications (see section 4.6).

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 to patients with hypersensitivity to other azoles

Cardiac effects

In a healthy volunteer study with itraconazole, a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. A similar investigation was not performed in the target patient population.

Itraconazole has been shown to have a negative inotropic effect and itraconazole has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.

Itraconazole should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk.

Physicians should carefully review the risks and benefits of itraconazole therapy for patients with known risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischaemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other oedematous 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.

Caution should be exercised when co-administering itraconazole and calcium channel blockers (see section 4.5).

Hepatic effects

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of itraconazole. Some of these cases involved patients with no pre-existing liver disease. Some of these cases have been observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving itraconazole treatment. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. In these patients treatment should be stopped immediately and liver function testing should be conducted. Most cases of serious hepatotoxicity involved patients who had pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking other hepatotoxic drugs.

Elderly

Since clinical data of the use of itraconazole in elderly patients are limited, it is advised to use itraconazole in these patients only if 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 (see section 4.4).

Hepatic impairment

Studies have not been conducted with intravenous itraconazole in patients with 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 to 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 metabolized 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 sections 4.2 and 5.2.).

Renal impairment

Hydroxypropyl-β-cyclodextrin, when administered intravenously, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment defined as creatinine clearance below 30 ml/min itraconazole is contraindicated (see sections 4.3 and 5.2).

Itraconazole IV should be used with caution in patients with a lesser degree of renal failure. In patients with mild or moderate renal impairment, serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to the oral capsule formulation (see section 4.4).

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.

Neuropathy

If neuropathy occurs that 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.

Interaction potential

Co-administration of specific drugs with itraconazole may result in changes in efficacy or safety of itraconazole and/or the co-administered drug. For example, the use of itraconazole with CYP3A4 inducing agents may lead to sub-therapeutic plasma concentrations of itraconazole and thus treatment failure. In addition, the use of itraconazole with some substrates of CYP3A4 can lead to increases in plasma concentrations of these drugs and to serious and/or potentially life threatening adverse events, such as QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. The prescriber should refer to the co-administered medicinal product information for further information regarding serious or life threatening adverse events that could occur in cases of increased plasma concentrations for that medication. For recommendations concerning the co-administration of medicinal products which are contraindicated, not recommended or recommended for use with caution in combination with itraconazole please refer to section 4.5.

Paediatric population

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

Excipients

This medicinal product contains approximately 177 mg sodium per dose, equivalent to 9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Itraconazole is mainly metabolized 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 strong 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.

Drugs that may decrease itraconazole plasma concentrations

Co-administration of itraconazole with strong enzyme inducers of CYP3A4 may decrease the exposure of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be reduced. Examples include:

- Antibacterials: isoniazid, rifabutin (see also under 'Drugs that may have their plasma concentrations increased by itraconazole'), rifampicin.
- Anticonvulsants: carbamazepine, (see also under 'Drugs that may have their plasma concentrations increased by itraconazole'), phenobarbital, phenytoin.
- Antivirals: efavirenz, nevirapine.
- Herbal medicine: *Hypericum perforatum* (St John's Wort).

Therefore, administration of strong enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these drugs should be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon co-administration, it is recommended that the antifungal activity should be monitored and the itraconazole dose increased as deemed necessary.

Drugs that may increase itraconazole plasma concentrations

Strong inhibitors of CYP3A4 may increase the exposure of itraconazole. Examples include:

Antibacterials: ciprofloxacin, clarithromycin, erythromycin.

Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir (see also under 'Drugs that may have their plasma concentrations increased by itraconazole'), ritonavir (see also under 'Drugs that may have their plasma concentrations increased by itraconazole') and telaprevir.

It is recommended that these drugs be used with caution when co-administered with itraconazole IV. It is recommended that patients who must take itraconazole

concomitantly with strong inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured.

Drugs that may have their plasma concentrations increased by itraconazole

Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of drugs metabolised by CYP3A4 and can inhibit the drug transport by P-glycoprotein which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are administered with itraconazole. The full inhibitory effect of itraconazole is obtained after steady state in plasma is reached (see section 5.2). The effects of itraconazole in increasing the AUC of other drugs can be as high as 11-fold, as seen with oral midazolam (a sensitive CYP3A4 substrate) when co-administered with itraconazole 200 mg/d. These elevated plasma concentrations are likely to increase or prolong both therapeutic and adverse effects of these drugs. CYP3A4-metabolized drugs 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. Full inhibitory effect is not obtained until itraconazole steady state has been reached which takes approximately 2-4 days for itraconazole IV (see section 5.2). 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.

The interacting drugs are categorized 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. 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’: It is recommended that 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 interacting drug 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 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 be measured.

Examples of drugs that may have their plasma concentrations increased by itraconazole presented by drug class with advice regarding co-administration with itraconazole:

Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**
Alpha Blockers		tamsulosin	
Analgesics		fentanyl	alfentanil, buprenorphine IV and sublingual, oxycodone, methadone[c], sufentanil
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin
Antibacterials	telithromycin, in subjects with severe renal impairment or severe hepatic impairment	rifabutin[a]	telithromycin
Anticoagulants and Antiplatelet Drugs	dabigatran, ticagrelor	apixaban, rivaroxaban	coumarins, cilostazol
Anticonvulsants		carbamazepine[a]	
Antidiabetics			repaglinide, saxagliptin
Antihelmintics and Antiprotozoals	halofantrine		praziquantel
Antihistamines	mizolastine, terfenadine	ebastine	bilastine
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)	eletriptan	

Drug Class	Contraindicated	Not Recommended	Use with Caution
Antineoplastics	irinotecan	axitinib, dabrafenib, dasatinib, ibrutinib, lapatinib, nilotinib, sunitinib, trabectedin	bortezomib, busulphan, docetaxel, erlotinib, gefitinib, imatinib, ixabepilone, ponatinib, trimetrexate, vinca alkaloids
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, oral midazolam, pimozide, quetiapine, sertindole, triazolam		alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, risperidone
Antivirals		simeprevir	maraviroc, indinavir[b], ritonavir[b], saquinavir
Beta Blockers			nadolol
Calcium Channel Blockers	bepridil, lercanidipine, nisoldipine	felodipine	other dihydropyridines, verapamil
Cardiovascular Drugs, Miscellaneous	aliskiren, ivabradine, ranolazine	riociguat	bosentan
Diuretics	eplerenone		
Gastrointestinal Drugs	cisapride, domperidone		aprepitant
Immunosuppressants		ciclesonide, everolimus,	budesonide, cyclosporine,

Drug Class	Contraindicated	Not Recommended	Use with Caution
		temsirolimus	dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus
Lipid Regulating Drugs	lovastatin, simvastatin	atorvastatin	
Respiratory Drugs		salmeterol	
SSRIs, Tricyclics and Related Antidepressants			reboxetine
Urological Drugs	darifenacin, fesoterodine, in patients with moderate to severe renal or moderate to severe hepatic impairment, sildenafil, when indicated for pulmonary arterial hypertension, solifenacin, in patients with severe renal or moderate to severe hepatic impairment, vardenafil, in men older than 75 years of age	tolterodine, vardenafil, in men 75 years of age and younger	fesoterodine, oxybutynin, sildenafil, when indicated for erectile dysfunction, solifenacin, tadalafil
Other	colchicine, in patients with renal or hepatic impairment	colchicine	alitretinoin (oral formulation), cinacalcet, tolvaptan
[a]See also under 'Drugs that may decrease itraconazole plasma concentrations' [b]See also under 'Drugs that may increase itraconazole plasma concentrations' [c] Torsade de pointes has been reported			

Drugs that may have their plasma concentrations decreased by itraconazole

Co-administration of itraconazole with the NSAID meloxicam may decrease the plasma concentration of meloxicam. It is recommended that meloxicam be used with caution when co-administered with itraconazole, including monitoring for any reduction in efficacy of meloxicam with adjustments to the dose as necessary.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, 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 shows reproduction toxicity (see section 5.3).

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. Itraconazole has been shown to cross the placenta in a rat model.

Women of childbearing potential

Women of childbearing potential receiving itraconazole 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 and must not be administered to lactating women. Breast-feeding is to be discontinued prior to taking itraconazole.

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 intravenous treatment identified from clinical trials and/or from spontaneous reporting were cough, diarrhoea, vomiting, nausea, rash, and oedema (including generalised oedema and face oedema). 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 one randomized, active controlled, open-label clinical trial with itraconazole intravenous involving 192 patients for empirical therapy of febrile neutropenia, 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).

Adverse Drug Reactions	
Blood and lymphatic system disorders	
Common	Granulocytopenia
Uncommon	Thrombocytopenia
Immune system disorders	
Common	Anaphylactoid reaction, Hypersensitivity*
Not known	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Metabolism and nutrition disorders	
Common	Hyperglycaemia, Hypomagnesaemia
Uncommon	Hyperkalaemia
Not known	Hypertriglyceridaemia
Psychiatric disorders	
Common	Confusional state
Nervous system disorders	
Common	Dizziness, Headache, Somnolence, Tremor
Uncommon	Hypoaesthesia, Dysgeusia
Eye disorders	

Common	Visual disturbances, (including diplopia and blurred vision)
Ear and labyrinth disorders	
Uncommon	Transient or permanent hearing loss*
Cardiac disorders	
Common	Cardiac failure, Tachycardia
Uncommon	Left ventricular failure
Not known	Congestive heart failure*
Vascular disorders	
Common	Hypertension, Hypotension
Respiratory, thoracic and mediastinal disorders	
Very common	Cough
Common	Pulmonary oedema, Dyspnoea
Uncommon	Dysphonia
Gastrointestinal disorders	
Very common	Diarrhoea, Vomiting, Nausea
Common	Constipation, Abdominal pain, Dyspepsia, Gastrointestinal disorder
Not known	Pancreatitis
Hepatobiliary disorders	
Common	Hepatitis, Jaundice, Hyperbilirubinaemia
Not known	Serious hepatotoxicity (including some cases of fatal acute liver failure)*
Skin and subcutaneous tissue disorders	
Very common	Rash
Common	Urticaria, Rash erythematous, Pruritus, Alopecia, Hyperhidrosis
Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Photosensitivity
Musculoskeletal and connective tissue disorders	
Common	Myalgia
Renal and urinary disorders	
Common	Renal impairment, Urinary incontinence

General disorders and administration site conditions	
Very common	Oedema (including generalised oedema and face oedema)
Common	Chest pain, Injection site inflammation, Pyrexia, Pain, Fatigue, Chills
Investigations	
Common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Blood urea increased, Gamma-glutamyltransferase increased, Urine analysis abnormal
Uncommon	Blood creatine phosphokinase increased, Hepatic enzyme 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 capsules.

Infections and infestations: Sinusitis, Upper respiratory tract infection, Rhinitis

Blood and lymphatic system disorders: Leukopenia

Metabolism and nutrition disorders: Hypokalaemia

Nervous system disorders: Peripheral neuropathy*, Paraesthesia

Ear and labyrinth disorders: Tinnitus

Gastrointestinal disorders: Flatulence

Hepatobiliary disorders: Hepatic failure*, Hepatic function abnormal

Musculoskeletal and connective tissue disorders: Arthralgia

Renal and urinary disorders: Pollakiuria

Reproductive system and breast disorders: Erectile dysfunction, Menstrual disorder

Paediatric population

The safety of itraconazole IV was evaluated in 36 paediatric patients aged 6 months to 17 years who participated in 3 open-label clinical trials. These patients received at least one dose of itraconazole IV for prevention or treatment of fungal infections and provided safety data.

Based on pooled safety data from these clinical trials, the very commonly reported adverse drug reactions (ADRs) in paediatric patients were pyrexia (16.7 %) and vomiting (11.1 %). The nature of ADRs in paediatric patients is similar to that observed in adult subjects, but in general, the incidence is higher in the adult subjects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

In general, adverse events reported with overdose have been consistent with adverse drug reactions already listed in this SmPC for itraconazole (see section 4.8).

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotic for systemic use, triazole derivatives, ATC code: J02A C02

Mechanism of action

Itraconazole inhibits fungal 14α-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-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 drugs has been observed within *Candida* species though resistance to one member of the class does not necessarily confer resistance to other azoles.

Breakpoints

Breakpoints for itraconazole have not yet been established for fungi using EUCAST methods.

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.

5.2 Pharmacokinetic properties

Itraconazole

General pharmacokinetic characteristics

Peak plasma concentrations of itraconazole are reached at the end of the intravenous infusion, declining thereafter. Peak plasma concentrations of hydroxy-itraconazole (see Biotransformation below) are reached within 3 hours of beginning of a one-hour infusion, declining thereafter.

As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing.

In 4 multiple-dose pharmacokinetic studies in patients, itraconazole IV was administered as a 1-hour infusion of 200 mg itraconazole twice daily on days 1 and 2 of treatment, followed by a 1-hour infusion of 200 mg once daily from day 3 to day 7. Steady-state plasma concentrations of itraconazole and hydroxy-itraconazole were generally reached within 48 and 96 hours, respectively. Itraconazole plasma concentrations > 250 ng/ml were achieved in most patients.

Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours after repeated dosing.

Each 200 mg intravenous dose of itraconazole contains 8 g hydroxypropyl-β-cyclodextrin to increase the solubility of itraconazole. The pharmacokinetic profile of this component is described below. (See Itraconazole; see section 5.1 ‘Hydroxypropyl-β-cyclodextrin’.)

Distribution

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

Concentrations in the cerebrospinal fluid are much lower than in the plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

Biotransformation

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 in 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

Studies have not been conducted with intravenous itraconazole in patients with 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 Cmax (47 %) and a two-fold 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

A small fraction (< 1 %) of an intravenous dose of itraconazole is excreted unchanged in urine.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50-79 ml/min), moderate (defined in this study as CrCl 20-49 ml/min), and severe renal impairment (defined in this study as CrCl < 20 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 sections 4.2, 4.3 and 4.4).

Paediatric population

Limited pharmacokinetic data are available on the use of itraconazole in the paediatric population. Clinical pharmacokinetic studies in children and adolescents aged between 5 months and 17 years were performed with itraconazole capsules, oral solution or intravenous formulation. Individual doses with the capsule and oral solution formulation ranged from 1.5 to 12.5 mg/kg/day, given as once-daily or twice-daily administration. The intravenous formulation was given either as a 2.5 mg/kg single infusion, or a 2.5 mg/kg infusion given once daily or twice daily. For the same daily dose,

twice daily dosing compared to single daily dosing yielded peak and trough concentrations comparable to adult single daily dosing. No significant age dependence was observed for itraconazole AUC and total body clearance, while weak associations between age and itraconazole distribution volume, Cmax and terminal elimination rate were noted. Itraconazole apparent clearance and distribution volume seemed to be related to weight.

Hydroxypropyl-ß-cyclodextrin

In patients with normal renal function, the pharmacokinetic profile of hydroxypropyl-ß-cyclodextrin, an ingredient of itraconazole intravenous formulation, has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority (> 85 %) of an 8 g dose of hydroxypropyl-ß-cyclodextrin is eliminated in the urine. Following a single intravenous dose of itraconazole 200 mg, clearance of hydroxypropyl-ß-cyclodextrin was reduced in subjects with renal impairment, resulting in higher exposure to hydroxypropyl-ß-cyclodextrin. In subjects with mild, moderate, and severe renal impairment, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropyl-ß-cyclodextrin until steady state is reached. Hydroxypropyl- ß-cyclodextrin is removed by haemodialysis.

5.3 Preclinical safety data

Itraconazole

Non-clinical 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.

Hydroxypropyl-ß-cyclodextrin

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. In a rat carcinogenicity study hydroxypropyl-β-cyclodextrin produced adenocarcinomas in the large intestine and exocrine pancreatic adenocarcinomas. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of the large intestine adenocarcinomas is low and the mechanism of exocrine pancreatic adenocarcinomas induction not considered relevant to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Itraconazole concentrate

Hydroxypropyl-β-cyclodextrin

Propylene glycol

Hydrochloric acid

Sodium hydroxide (for pH adjustment)

Water for injections

Sodium Chloride 0.9 % w/v solution for infusion

Sodium chloride

Water for injections

6.2 Incompatibilities

Itraconazole has the potential to precipitate when Itraconazole concentrate is diluted in solutions other than the 50 ml Sodium Chloride 0.9 % w/v solution for infusion supplied.

6.3 Shelf life

Itraconazole concentrate

18 months

Sodium Chloride 0.9 % w/v solution for infusion

12 months

Admixed Solution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8 °C. From a microbiological point of view the prepared infusion should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user.

Protect from direct sunlight.

6.4 Special precautions for storage

Itraconazole concentrate

Do not store above 25 °C.

Keep the ampoule in the outer carton in order to protect from light.

Do not freeze.

Sodium Chloride 0.9 % w/v solution for infusion

Do not store above 25 °C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Itraconazole concentrate

25 ml siliconised type I colourless glass ampoule with 25 ml containing 250 mg itraconazole.

Sodium Chloride 0.9 % w/v solution for infusion

Flexible polypropylene infusion bag, equipped with a flexible inlet and outlet port, and containing 50 ml of Sodium Chloride 0.9 % w/v solution for infusion.

Extension line

PVC tubing with 2-way stopcock and in-line filter.

6.6 Special precautions for disposal

Itraconazole has the potential to precipitate when 25 ml of Itraconazole concentrate are diluted in solutions other than 50 ml Sodium Chloride 0.9 % w/v solution for infusion. The full amount of 25 ml of Itraconazole concentrate from the ampoule must be diluted into the Sodium Chloride Infusion Bag, which is intended to be used exclusively in combination with Itraconazole concentrate. Only the components of a unit sales pack (e.g. saline bag, an extension line with a 2-way stopcock and 0.2 µm in-line filter, and Itraconazole ampoule) must be used. Itraconazole cannot be co-administered with other drugs or fluids (see section 6.2).

Prior to starting the admixing process, the Itraconazole concentrate and the solvent (Sodium Chloride) must be visually inspected. Only clear solutions free from foreign particles should be used for the preparation of the admixture.

The full amount of Itraconazole concentrate must be injected into the Sodium Chloride bag in a slow single action (up to 60 seconds). During the admixing process opalescence may appear but will clear after gently mixing. When visually inspecting the bag after admixing and prior to administration, product intrinsic aggregates may be observed. These aggregates do not affect the quality of the product. The dedicated extension line with the 0.2 µm in-line filter must be used to prevent aggregates from reaching the recipient's circulation.

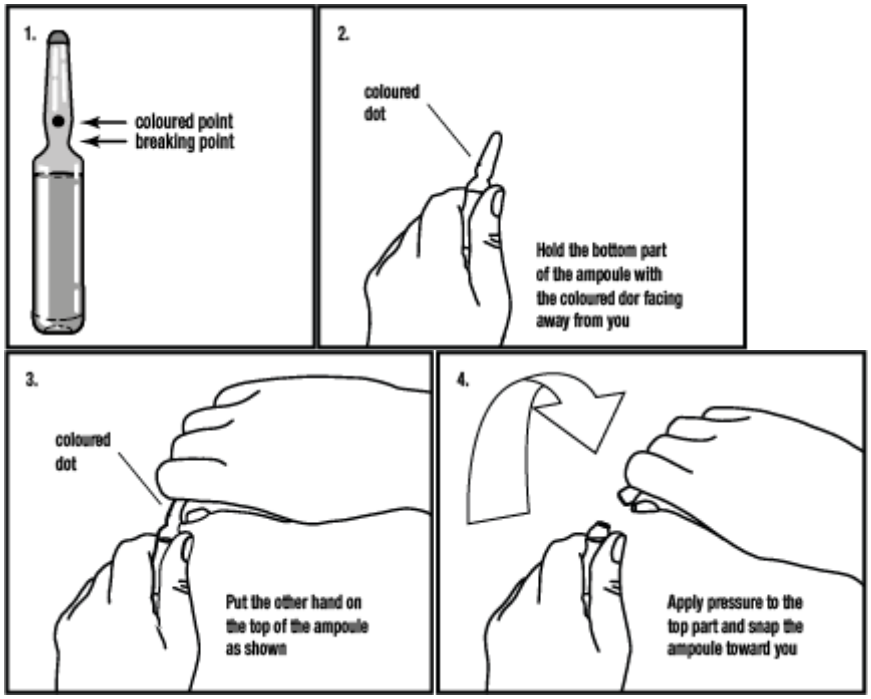
Itraconazole should be prepared for administration according to the following instructions:

Opening sodium chloride bag:

Tear outer wrap at notch and remove infusion bag.

Opening ampoule:

Break the ampoule as shown:



The admixing should begin immediately after opening the ampoule.

Flush procedure before the infusion:

Before the infusion, the catheter should be flushed to avoid compatibility problems between residual amounts of other drugs and itraconazole.

- Fill the extension line provided with the kit containing the 0.2 µm in-line filter with sterile Sodium Chloride 0.9 % w/v solution and connect directly to the indwelling intravenous catheter.
- Flush the extension line provided with the kit and indwelling intravenous catheter with sterile Sodium Chloride 0.9 % w/v solution.

Admixing Itraconazole concentrate and Sodium Chloride 0.9 % w/v solution for infusion:

- Each component must be at room temperature.
- Admix only in the infusion bag provided.
- Using aseptic technique and an additive delivery needle of appropriate length (not supplied with the kit), draw up all the concentrate from the ampoule and subsequently add the Itraconazole concentrate to the infusion bag by puncturing the resealable additive port and inject.
- Add the entire volume (25 ml) of Itraconazole concentrate while holding the bag in upright position in a slow single action (up to 60 seconds), this approach will avoid the concentrate collecting in the tubing which would hinder proper mixing. During the admixing process some opalescence may appear. This is a normal phenomenon for the product and will disappear after the full content of the 25 ml of Itraconazole has been diluted into the Sodium Chloride infusion bag and after gentle mixing. Withdraw needle after injecting the Itraconazole concentrate into the bag.
- Gently mix the content of the bag once the Itraconazole concentrate is completely transferred to the bag. The admixture will become clear but product intrinsic aggregates (described as fibrous to flake-like, non-crystalline, white particles) may be observed. These aggregates do not affect the quality of the product.
- The admixture should be used immediately and should be protected from direct sunlight. During administration, exposure to normal room light is acceptable (see sections 6.3 and 6.4 of the SmPC).

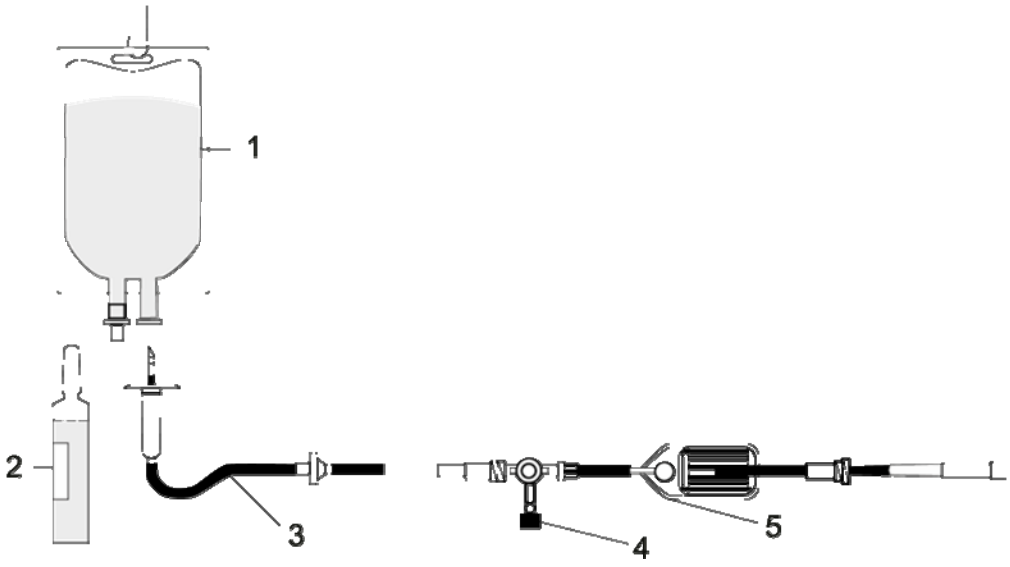
Infusion:

- The admixed solution is intended for single-dose infusion only. No administration should occur if the solution is a milky white colour that does not disappear after gentle mixing, or contains foreign matter, or if the infusion bag is damaged.
- The infusion bag should now contain 25 ml Itraconazole concentrate and 50 ml Sodium Chloride 0.9 % w/v solution for infusion.
- Note: An infusion line with drip chamber is not supplied with the kit. Close the flow control device (e.g., rotary clamp) on the infusion line. Remove the breakable part of the outlet port. Using aseptic technique, push the pin of the infusion line in the flexible port of the infusion bag.
- Slowly release the flow control device and fill the drip chamber to half full by squeezing (pumping) it.
- Open the flow control device until all the air has been expelled from the infusion line.
- Connect the infusion line to the two-way stopcock of the extension line.
- The Itraconazole infusion is now ready for intravenous infusion to the patient.

- Adjust the infusion rate to 1 ml/min (approximately 25 drops/min) by means of a flow control device (e.g. rotary clamp or infusion pump).
- Administer 60 ml of the solution to the patient over approximately one hour.
- Stop the infusion when 60 ml is administered.
- Note that 200 mg of itraconazole has been administered.
- Flush the line as per the flushing procedure described below.

Flush procedure after the infusion:

- After the infusion a complete flush procedure must be started to clean the catheter. This is done to avoid compatibility problems between residual amounts of itraconazole and other drugs which later could be administered through the same catheter.
- Flush the extension line and catheter with 15–20 ml of sterile Sodium Chloride 0.9 % w/v solution at the level of the 2-way stop cock, just before the 0.2 µm in-line filter.
- Perform the flush in a continuous run of 30 seconds to 15 minutes.
- After flushing, disconnect and discard the bag, the infusion line and the extension line.
- Do not re-sterilise or re-use the Itraconazole infusion set.
- To avoid precipitation, other medication should only be administered via the catheter after flushing.
- If using a multi-lumen catheter, other medication may not be administered until the Itraconazole infusion has been completed and the catheter has been flushed.



1. Sodium Chloride infusion bag
2. Itraconazole ampoule
3. Infusion line with drip chamber (not provided)

4 & 5. Extension line with 2-way stopcock and in-line filter.

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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