SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Itraconazole 10mg/ml Sugar Free Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 10mg itraconazole.

Excipient(s) with known effect:
Each ml of oral solution contains 171.97mg sorbitol (E420),0.7124mg sodium, 400mg cyclodextrins (E459) and 40.92mg propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

Itraconazole oral solution is clear, colourless to yellow colour solution with an odour of cherry.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Itraconazole oral solution is indicated:

For the treatment of oral and/or oesophageal candidosis in HIV-positive or other immunocompromised patients.

As prophylaxis of deep fungal infections anticipated to be susceptible to itraconazole, when standard therapy is considered inappropriate, in patients with haematological malignancy or undergoing bone marrow transplant, and who are expected to become neutropenic (ie < 500 cells/µl). At present there are insufficient clinical efficacy data in the prevention of aspergillosis.

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

4.2 Posology and method of administration

For optimal absorption, Itraconazole oral solution should be taken without food (patients are advised to refrain from eating for at least 1 hour after intake).

For the treatment of oral and/or oesophageal candidosis, the liquid should be swished around the oral cavity (approx. 20 seconds) and swallowed. There should be no rinsing after swallowing.

Treatment of oral and/or oesophageal candidosis:
200mg (20ml) per day in two intakes, or alternatively in one intake, for 1 week. If there is no response after 1 week, treatment should be continued for another week.

Treatment of fluconazole resistant oral and/or oesophageal candidosis:
100 to 200mg (10-20ml) twice daily for 2 weeks. If there is no response after 2 weeks, treatment should be continued for another 2 weeks. The 400mg (40ml) daily dose should not be used for longer than 14 days if there are no signs of improvement.

Prophylaxis of fungal infections:
5mg/kg (0.5ml/kg) per day administered in two intakes. In clinical trials, prophylaxis treatment was started immediately prior to the cytostatic treatment and generally one week before transplant procedure. Almost all proven deep fungal infections occurred in patients reaching neutrophil counts below 100 cells/µl. Treatment was continued until recovery of neutrophils (i.e. > 1000 cells/µl).

Pharmacokinetic parameters from clinical studies in neutropenic patients demonstrate considerable intersubject variation. Blood level monitoring should be considered particularly in the presence of gastrointestinal damage, diarrhoea and during prolonged courses of Itraconazole oral solution.

Use in patients with gastro-intestinal motility impairment
When treating patients with severe fungal infections or when administering it as fungal prophylaxis to those with abnormal gastro-intestinal motility, patients should be carefully monitored and where appropriate drug therapeutic monitoring should be considered, where available.

Paediatric population
The safety and efficacy of Itraconazole oral solution in children has not been established. Currently available data are described in section 4.4 and 5.2 but no recommendation on a posology can be made.

The use of Itraconazole oral solution in paediatric patients is not recommended unless it is determined that 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 5mg/kg (0.5ml/kg) per day administered in two intakes (see section 4.8).

Use in elderly
Since clinical data on the use of Itraconazole oral solution in elderly patients are limited, it is advised to use Itraconazole oral solution in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an 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).

Use 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 this drug is administered in this patient population (see section 5.2).

Use in patients with 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 and a wide inter-subject variation was observed in these subjects receiving the capsule formulation (see section 5.2). Caution should be exercised when this drug is administered in this patient population and adjusting the dose or switching to an alternative antifungal medication may be considered based on an evaluation of clinical effectiveness.

4.3 Contraindications

- Itraconazole oral solution is contraindicated in patients with a known hypersensitivity to itraconazole or to any of the excipients.
- Itraconazole oral solution 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 oral solution must not be used during pregnancy for non life-threatening indications (see section 4.6).
- Co-administration of a number of CYP3A4 substrates is contraindicated with Itraconazole oral solution (see sections 4.4 and 4.5). These include:

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	
Bepridil	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	
Immunosuppresants			
Voclosporin			
Lipid Modifying Agents			
Lovastatin	Lomitapide		Simvastatin
Psychoanaleptics; Psycholeptics (eg, 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).		

4.4 Special warnings and precautions for use

Use in patients with gastro-intestinal motility impairment
When treating patients with severe fungal infections or when administering it as fungal prophylaxis to those with abnormal gastro-intestinal motility, patients should be carefully monitored and where appropriate drug therapeutic monitoring should be considered, where available.

Cross-hypersensitivity
There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing Itraconazole oral solution to patients with hypersensitivity to other azoles.

Cardiac effects
In a healthy volunteer study with Itraconazole IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed.

Itraconazole has been shown to have a negative inotropic effect and Itraconazole has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400mg (40ml) total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.

Itraconazole should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dose and duration of treatment, and individual risk factors for congestive heart failure. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, Itraconazole should be discontinued.

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.

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

Use in elderly
Since clinical data on the use of Itraconazole oral solution in elderly patients is limited, it is advised to use Itraconazole oral solution 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
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. 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. The exposure of itraconazole may be lower in some patients with renal insufficiency and a wide inter-subject variation was observed in these subjects receiving the capsule formulation (see section 5.2). Caution should be exercised when this drug is administered in this patient population and adjusting the dose or switching to an alternative antifungal medication may be considered based on an evaluation of clinical effectiveness.

Prophylaxis in neutropenic patients
In clinical trials diarrhoea was the most frequent adverse event. This disturbance of the gastrointestinal tract may result in impaired absorption and may alter the microbiological flora potentially favouring fungal colonisation. Consideration should be given to discontinuing Itraconazole oral solution in these circumstances.

Treatment of severely neutropenic patients
Itraconazole oral solution as treatment for oral and/or oesophageal candidosis was not investigated in severely neutropenic patients. Due to the pharmacokinetic properties (see section 5.2), Itraconazole oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidosis.

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.

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 oral solution, consideration should be given to switching to Itraconazole IV or to alternative therapy.

Neuropathy
If neuropathy occurs that may be attributable to Itraconazole oral solution, 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 sections 4.3 and 4.5.

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.

Excipients Warnings
Sorbitol (E420): This medicinal product contains 6878.76 mg sorbitol in each 40 ml dose which is equivalent to 171.97 mg/ml. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Sodium: This medicinal product contains 1.2mmol (or 28.45mg) sodium per 40 ml, equivalent to 1.43% of the WHO recommended maximum daily intake of 2g sodium for an adult.

Cyclodextrins (E459): This medicinal product contains 16000 mg cyclodextrin(s) in each 40 ml dose which is equivalent to 400 mg/ml. Cyclodextrins (CDs) are excipients which can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC. Cyclodextrins may cause digestive problems such as diarrhoea.

Propylene glycol (E1520): This medicinal product contains 1636.8mg propylene glycol in each 40 ml dose which is equivalent to 40.92mg/ml.

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. Please refer to the prescribing information of the interacting drug for more information.

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

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 info 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 (*Hypericum perforatum*)	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

Medicinal products (PO Single Dose unless otherwise stated) within class	**Expected/Potential effect on drug levels**	**Clinical comment**
	(↑ = increase; ↔ = no change; ↓ = decrease)	**(see above for additional info and also sections 4.3 and 4.4)**
Analgesics; Anaesthetics		
Ergot alkaloids (e.g., dihydroergotamine, ergometrine, ergotamine, methylergometrine)	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, vinorelbine)	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
Cobimetinib 10 mg	Cobimetinib C_{max} ↑ 3.2-fold, AUC ↑ 6.7-fold	Not recommended
Entrectinib	Entrectinib Cmax ↑ 73%, AUC ↑ 6.0 fold	Not recommended
Olaparib 100 mg	Olaparib C_{max} ↑ 40%, AUC ↑ 2.7-fold	Not recommended
Talazoparib	Talazoparib Cmax ↑ 40%, AUC ↑ 56%	Not recommended

Alitretinoin (oral), Bortezomib, Brentuximab vedotin, Erlotinib, Idelalisib, Imatinib, Nintedanib, Panobinostat, Ponatinib, Ruxolitinib, Sonidegib,	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 Cmax ↑ 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, Dronedarone, 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 bosentan.	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 aprepitant.	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 cyclosporine.	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 84 mg/day should be considered.
Cinacalcet	Although not studied directly, itraconazole is likely to increase the concentrations of cinacalcet.	Use with caution

4.6 Fertility, pregnancy and lactation

Pregnancy
Itraconazole oral solution must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see section 4.3).

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

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 taking Itraconazole oral solution should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Itraconazole therapy.

Breast-feeding
A very small amount of itraconazole is excreted in human milk. Itraconazole oral solution must not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual 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 oral solution treatment identified from clinical trials and/or from spontaneous reporting were dizziness, headache, dysgeusia, dyspnoea, cough, abdominal pain, diarrhoea, vomiting, nausea, dyspepsia, rash, and pyrexia. 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 double-blind and open-label clinical trials with Itraconazole oral solution involving 889 patients for the treatment of oropharyngeal and esophageal candidiasis, 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	
Uncommon	Leukopenia, Thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity*
Not Known	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Endocrine disorders	
Not known	Pseudoaldosteronism
Metabolism and nutrition disorders	
Uncommon	Hypokalaemia
Not Known	Hypertriglyceridaemia
Nervous system disorders	
Common	Dizziness, Headache, Dysgeusia
Uncommon	Peripheral neuropathy*, Paraesthesia, Hypoaesthesia
Eye disorders	
Uncommon	Visual disturbances (including diplopia and blurred vision)
Ear and labyrinth disorders	
Uncommon	Tinnitus
Not Known	Transient or permanent hearing loss*
Cardiac disorders	
Uncommon	Cardiac failure
Not Known	Congestive heart failure*
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, Cough
Gastrointestinal disorders	
Common	Abdominal pain, Diarrhoea, Vomiting, Nausea, Dyspepsia
Uncommon	Constipation
Not Known	Pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic failure*, Hyperbilirubinaemia
Not Known	Serious hepatotoxicity (including some cases of fatal acute liver failure)*
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Urticaria, Pruritus
Not Known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia, Arthralgia
Reproductive system and breast disorders	
Uncommon	Menstrual disorders
General disorders and administration site conditions	
Common	Pyrexia
Uncommon	Oedema

Investigations	
Not Known	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 Capsules and Itraconazole IV, excluding the ADR term "Injection site inflammation", which is specific to the injection route of administration.

Infections and infestations: Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and lymphatic system disorders: Granulocytopenia
Immune system disorders: Anaphylactoid reaction
Metabolism and nutrition disorders: Hyperglycaemia, Hyperkalaemia, Hypomagnesaemia
Psychiatric disorders: Confusional state
Nervous system disorders: Somnolence, Tremor
Cardiac disorders: Left ventricular failure, Tachycardia
Vascular disorders: Hypertension, Hypotension
Respiratory, thoracic and mediastinal disorders: Pulmonary oedema, Dysphonia
Gastrointestinal disorders: Gastrointestinal disorder, Flatulence
Hepatobiliary disorders: Hepatitis, Jaundice, Hepatic function abnormal
Skin and subcutaneous tissue disorders: Rash erythematous, Hyperhidrosis
Renal and urinary disorders: Renal impairment, Pollakiuria, Urinary incontinence
Reproductive system and breast disorders: Erectile dysfunction
General disorders and administration site conditions: Generalised oedema, Face oedema, Chest pain, Pain, Fatigue, Chills
Investigations: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Blood urea increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Urine analysis abnormal

Paediatric Population

The safety of Itraconazole oral solution was evaluated in 250 paediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least one dose of Itraconazole oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data.
Based on pooled safety data from these clinical trials, the very common reported ADRs in paediatric patients were Vomiting (36.0%), Pyrexia (30.8%), Diarrhoea (28.4%), Mucosal inflammation (23.2%), Rash (22.8%), Abdominal pain (17.2%), Nausea (15.6%), Hypertension (14.0%), and Cough (11.2%). The nature of ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal

product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website 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).

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotic for systemic use, triazole and tetrazole derivative.
ATC code: J02A C02

Mechanism of action
Itraconazole inhibits fungal 14-alpha-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 been established in the European Committee on Antimicrobial Susceptibility Testing
(EUCAST) breakpoints for antifungal agents, version 10.0, valid from 2020-02-04.

Candida and Aspergillus species	**Minimal Inhibitory Concentration (MIC) breakpoint (mg/L)**	
	≤ S (Susceptible)	**> R (Resistant)**
Candida albicans	0.06	0.06
Candida dubliniensis	0.06	0.06

Candida parapsilosis	0.125	0.125
Candida tropicalis	0.125	0.125
Aspergillus flavus[1,2]	1	1
Aspergillus fumigatus[1,2]	1	1
Aspergillus nidulans[1,2]	1	1
Aspergillus terreus[1,2]	1	1

There is currently insufficient evidence to set clinical breakpoints for *Candida glabrata*[3], *C. krusei*[3], *C. guilliermondi*[3], *Cryptococcus neoformans*, and Non- species related breakpoints for *Candida.*
There is currently insufficient evidence to set clinical breakpoints for *Aspergillus niger*[4,5] and Non□species related breakpoints for *Aspergillus spp.*[5].

[1] Monitoring of azole trough concentrations in patients treated for fungal infection is recommended.
[2] Area of technical uncertainty (ATU) is 2. Report as R with the following comment: "In some clinical situations (non-invasive Infections forms) itraconazole can be used provided sufficient exposure is ensured".
[3] The epidemiological cut-off values (ECOFFs) for these species are in general higher than for *C. albicans.*
[4] The epidemiological cut-off values (ECOFFs) for these species are in general one two-fold dilution higher than for *A. fumigatus.*
[5] The MIC values for isolates of *A. niger* and *A. versicolor* are in general higher than those for A. fumigatus. Whether this translates into a poorer clinical response is unknown.

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 for Antifungal Susceptibility Testing of Yeasts. 2nd 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 of itraconazole may vary widely. Susceptibility in the table below is based on MIC_{90} < 1mg 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]
Talaromyces (formerly Penicillium) marneffei[1]
Pseudallescheria boydii
Sporothrix schenckii
Trichophyton spp.
Trichosporon spp.
Species for which acquired resistance may be a problem
Candida glabrata [3]
Candida krusei
Candida tropicalis [3]
Inherently resistant organisms
Absidia spp.
Fusarium spp.
Mucor spp.
Rhizomucor spp.
Rhizopus spp.
Scedosporium proliferans
Scopulariopsis spp.

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

Paediatric Population
The tolerability and safety of itraconazole oral solution was studied in the prophylaxis of fungal infections in 103 neutropenic paediatric patients aged 0 to14 years (median 5 years) in an open-label uncontrolled phase III clinical study. Most patients (78%) were undergoing allogenic bone marrow transplantation for haematological malignancies. All patients received 5mg/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

Itraconazole
General pharmacokinetic characteristics
Peak plasma concentrations are reached within 2.5 hours following administration of the oral solution. 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} and AUC values 4 to 7-fold higher than those seen after a single dose. Steady-state C_{max} values of about 2µg/ml are reached after oral administration of 200mg once daily. 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 278ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Absorption
Itraconazole is rapidly absorbed after administration of the oral solution. Peak plasma concentrations of itraconazole are reached within 2.5 hours following administration of the oral solution under fasting conditions. The observed absolute bioavailability of itraconazole under fed conditions is about 55% and increases by 30% when the oral solution is taken in fasting conditions. Itraconazole exposure is greater with the oral solution than with the capsule formulation when the same dose of drug is given (see section 4.4).

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 (>700L), 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, 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 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
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 average C_{max} (47%) and a two-fold increase in the elimination half-life (37 ± 17 versus 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. 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 (uraemia: n=7; haemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13ml/min. × 1.73m^2, the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of haemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max}, C_{max}, and AUC_{0-8h}). 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 CrCl 50-79ml/min), moderate (defined in this study as CrCl 20-49ml/min), and severe renal impairment (defined in this study as CrCl <20ml/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 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 5mg/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.

Hydroxypropyl-β-Cyclodextrin
The oral bioavailability of hydroxypropyl-β-cyclodextrin given as a solubilizer of itraconazole in oral solution is on average lower than 0.5% and is similar to that of hydroxypropyl-β-cyclodextrin alone. This low oral bioavailability of hydroxypropyl-β-cyclodextrin is not modified by the presence of food and is similar after single and repeated administrations.

5.3 Preclinical safety data

Itraconazole
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 mg/m2/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 mg/m^2), 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 (2-fold of

MRHD based on mg/m ^{2}), 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-β-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 (at 80 mg/kg dose (2-fold of MRHD based on mg/m^2)), 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.

Reproductive toxicology
Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats and mice at 40, 80 and 160 mg/kg (0.5-, 1- and 4-fold of MRHD based on mg/m^2). 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 dose (4-fold of MRHD based on mg/m^2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl-β-cyclodextrin (E459)

Sorbitol, liquid (non-crystallising) (E420)

Propylene glycol (E1520)

Sodium saccharin (E954)

Concentrated hydrochloric acid (E507)

Cherry flavor (containing propylene glycol (E1520))

Sodium hydroxide (for pH adjustment)

Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months

Discard 30 days after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

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

6.5 Nature and contents of container

Bottle: Ph. Eur. Type III amber colour glass bottles

Closure: Tamper evident, child resistant white plastic cap consists of polypropylene inner, polyethylene outer, expanded polyethylene (EPE) liner

Dosing device: 30ml measuring cup with 5ml graduation (including 2.5ml and 7.5ml intermediate graduation)

Pack size: 150ml

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Syri Limited

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Ruislip, Middlesex,

HA4 0NU, UK

Trading as:

Thame Laboratories,

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OR

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8 MARKETING AUTHORISATION NUMBER(S)

PL 39307/0069

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/04/2022

10 DATE OF REVISION OF THE TEXT

05/02/2025