Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Itraconazole 10mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml Itraconazole oral solution contains 10mg itraconazole.

Excipients with known effect:
Each ml of Itraconazole oral solution contains 283.1mg of sorbitol E420, 103.6mg of propylene glycol (E 1520), less than 100mg of Ethanol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Itraconazole oral solution is a clear, yellow solution.

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 (i.e. < 500 cells/microlitre). At present there are insufficient clinical efficacy data in the prevention of aspergillosis.

Itraconazole oral solution is indicated for use in adults.

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).

A graduated measuring cup is provided to measure out the correct dose.

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: 200 mg (20 ml) 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 200 mg (10-20 ml) twice daily for 2 weeks. If there is no response after 2 weeks, treatment should be continued for another 2 weeks. The 400mg daily dose should not be used for longer than 14 days if there are no signs of improvement.

Prophylaxis of fungal infections: 5 mg/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/microlitre. Treatment was continued until recovery of neutrophils (i.e. > 1000 cells/microlitre).

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.

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

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

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).

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 listed in section 6.1.

Co-administration of a number of CYP3A4 substrates is contraindicated with Itraconazole Oral Solution (see sections 4.4 and 4.5).

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 Special warnings and precautions).

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

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 has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400mg 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 oral solution 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 the 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 oral solution 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.

Use in children
Since clinical data on the use of Itraconazole oral solution in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks.

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 4.2).

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 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 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 intersubject 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 esophageal candidosis was not investigated in severely neutropenic patients. Due to the pharmacokinetic properties (See 5.2 Pharmacokinetic properties), 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.

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
Itraconazole Oral Solution has a potential for clinically important drug interactions (see section 4.5).

Itraconazole should not be used within 2 weeks after discontinuation of treatment with CYP 3A4 inducing agents (rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine, *Hypericum perforatum* (St. John´s wort)). The use of itraconazole with these drugs may lead to subtherapeutic plasma levels of itraconazole and thus treatment failure. 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.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. This medicine contains small amounts of ethanol (alcohol), less than 100mg per dose, 2,080mg propylene glycol per 20 mil solution (maximum single dose) which is equivalent to 103.6 mg/ml and less than 1mmol sodium (23mg) per mil, that is to say essentially "sodium free".".

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction (see section 4.8 Undesirable effects).

4.5 Interaction with other medicinal products and other forms of interactions

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 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 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 oral solution. 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 the 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 the cytochrome 3A family (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 effect 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 200mg/ 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 around 15 days for Itraconazole Oral Solution (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	levacetylmethadol	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	rivaroxaban apixaban,	coumarins, cilostazol
Anticonvulsants		carbamazepine[a]	
Antidiabetics			repaglinide, saxagliptin
Antihelmintics and Antiprotozoals	halofantrine		praziquantel
Antihistamines	mizolastine, terfenadine astemizole	ebastine	bilastine
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)	eletriptan	
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	oral midazolam,		alprazolam,
	pimozide**,**		aripiprazole,
	quetiapine,		brotizolam,
	sertindole,		buspirone,
	triazolam		haloperidol,
	lurasidone,		midazolam IV,
			perospirone,
			risperidone
Antivirals		simeprevir	maraviroc,
			indinavir[b],
			ritonavir[b],
			saquinavir
Beta Blockers			nadolol
Calcium Channel Blockers	bepridil,	felodipine	other dihydropyridines, including verapamil
	lercanidipine,		
	nisoldipine		
Cardiovascular Drugs, Miscellaneous	aliskiren,	riociguat	bosentan
	ivabradine,		
	ranolazine		
Diuretics	eplerenone		
Gastrointestinal Drugs	cisapride		aprepitant
	domperidone		
Immunosuppressants		ciclesonide,	budesonide,
		everolimus,	ciclosporine,
		temsirolimus	dexamethasone,
			fluticasone,
			methylprednisolone,
			rapamycin (also known as sirolimus),
			tacrolimus
Lipid Regulating Drugs	lovastatin,	atorvastatin	
	simvastatin		
Respiratory Drugs		salmeterol	
SSRIs, Tricyclics and Related Antidepressants			reboxetine
Urological Drugs	darifenacin	tolterodine,	oxybutynin,
	fesoterodine, in patients with moderate to severe renal or moderate to severe hepatic impairment,		fesoterodine.
	sildenafil, when indicated for pulmonary arterial hypertension,	vardenafil, in men 75 years of age and younger	sildenafil, when indicated for erectile dysfunction,
	solifenacin, in patients with severe renal or moderate hepatic impairment,		solifenacin,
	vardenafil, in men older than 75 years of age		tadalafil
Other	colchicine, in patients with renal or hepatic impairment	colchicine	alitretinoin (oral formulation),
			cinacalcet,
			tolvaptan
			loperamide

[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

Caution should be exercised when co-administering itraconazole with calcium channel blockers due to an increased risk of congestive heart failure. In addition to possible pharmacokinetic interactions involving the drug metabolising enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole.

No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed.
No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

Effect on protein binding:
In vitro studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indometacin, tolbutamide and sulfamethazine.

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 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 child-bearing potential:
Women of childbearing potential taking Itraconazole oral solution should use contraceptive precautions. Effective contraception should be continued until the next menstrual period following the end of Itraconazole therapy.

Fertility:
In the rat, itraconazole had no effect on male or female fertility at doses which exhibited signs of general toxicity. The effect in humans is unknown.

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 Undesirable effects), 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 involving 889 patients for the treatment of oropharyngeal and oesophageal candidiasis, and from spontaneous reporting.

The table below presents adverse drug reactions by System Organ Class. Within each System Organ Class, the adverse drug reactions are presented by incidence, using the following convention:
Very common (≥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	Leucopenia, Neutropenia, Thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity*
Not Known	Serum Sickness, Angioneurotic Oedema, Anaphylactic Reaction, Anaphylactoid Reaction,
Metabolism and nutrition disorders	
Uncommon	Hypokalaemia
Not Known	Hypertriglyceridemia
Nervous system disorders	
Common	Headache, Dizziness, Dysgeusia
Uncommon	Peripheral Neuropathy*, Paraesthesia, Hypoaesthesia
Eye disorders	
Uncommon	Visual Disorders, including Vision Blurred and Diplopia
Ear and labyrinth disorder	
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, Vomiting, Nausea, Diarrhoea, Dyspepsia
Uncommon	Constipation
Not Known	Pancreatitis
Hepato-biliary disorders	
Uncommon	Hepatic failure*, Hyperbilirubinaemia
Not Known	Serious Hepatotoxicity* including some cases of fatal Acute hepatic 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.

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 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 following:

IE: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotic for systemic use, triazole derivative.
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.

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 5 mg/kg/day of itraconazole oral solution as a single or divided dose. Due to the design of the study, no formal conclusion with regard to efficacy could be derived. The most common adverse events considered definitely or possibly related to itraconazole were vomiting, abnormal liver function, and abdominal pain.

5.2 Pharmacokinetic properties

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 2 microgram/ml are reached after oral administration of 200 mg 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 278 ml /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 the unchanged drug are reached within 2.5 hours following an oral dose 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 (> 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 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. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole. Trough plasma concentrations of the hydroxy-itraconazole are about twice those of itraconazole.
As shown in *in vitro* studies, CYP 3A4 is the major enzyme that is involved in the metabolism of itraconazole.

Elimination
Itraconazole is excreted mainly as inactive metabolites to about 35% in urine and to about 54% with faeces 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 radiolabeled 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 using a single 100 mg dose of itraconazole (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. 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 (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 ml/min. × 1.73 m2, the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (Tmax, Cmax, and AUC0-8h). 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 50-79 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 and 4.4).

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

Hydroxypropyl-ß-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

Nonclinical data on itraconazole revealed no indications for genotoxicity, 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-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 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

Hydroxypropyl-β-cyclodextrin
Sorbitol 70% (E420)
Propylene glycol
Cherry flavour
Caramel (contains ethanol and propylene glycol)
Sodium saccharin dihydrate
Hydrochloric acid and 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

18 months as packaged for sale.
1 month after first opening the container.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Type III 150 ml amber glass bottle, with child resistant polyethylene screw cap and LDPE internal coating, in a cardboard carton.

A graduated measuring cup is provided. Graduation is from 2.5 - 30ml, initially in 2.5ml and then 5ml intervals.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Athlone Laboratories Ltd
Ballymurray
Co. Roscommon
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0298/023/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 10th May 2013
Date of Last Renewal: 5th February 2018

10 DATE OF REVISION OF THE TEXT

November 2019