HEALTH CARE FORMULATIONS PVT. LTD.	
BRAND NAME:	**ITRACONAZOLE CAPSULES BP 200MG**

MODULE 1 ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCTCHARACTERISTICS

1. Name of the medicinal product

ITRACONAZOLE (ITRACONAZOLE CAPSULES BP 200MG)

2. Qualitative and quantitative composition

Each hard gelatin capsules contains:
Itraconazole Pellets
Eq to Itraconazole BP 200 mg
Excipients q.s.
Approved color used in empty capsule shell.

3. Pharmaceutical form

Each Hard Gelatin Capsule Size "0" Blue / White Cap / Body Containing White to Off white Pellets

4. Clinical particulars

4.1 Therapeutic indications

- Vulvovaginal candidosis,

- Oropharyngeal candidosis,

- Dermatophytoses caused by organisms susceptible to itraconazole (Trichophyton spp., Microsporumspp., Epidermophyton floccosum) e.g. tinea pedis, tinea cruris, tinea corporis, tinea manuum,

- Pityriasis versicolor,

- Onychomycosis caused by dermatophytes and/or yeasts,

- The treatment of histoplasmosis,

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

- Treatment of cryptococcosis (including cryptococcal meningitis). In immunocompromised patients suffering from cryptococcosis and in all patients with cryptococcosis of the central nervous system,

- Treatment of aspergillosis and candidosis.

- Maintenance therapy in AIDS patients to prevent relapse of underlying fungal infection.

Itraconazole capsules are also indicated in the prevention of fungal infection during prolonged neutropeniawhen standard therapy is considered inappropriate.

4.2 Posology and method of administration

Posology

Treatment schedules in adults for each indication are as follows:

INDICATIONS	DOSE	**DURATION OF TREATMENT**	**REMARKS**
- Vulvovaginal candidosis	200 mg b.i.d.[1]	1 day	
- Pityriasis versicolor	200 mg o.d.	7 days	
- Tinea corporis, tinea cruris	100 mg o.d. or 200 mg o.d.	15 days or 7 days1	
- Tinea pedis, tinea manuum	100 mg o.d.	30 days	
- Oropharyngeal candidosis	100 mg o.d.	15 days	Increase dose to 200 mg once daily for 15 days in AIDS or neutropenic patients because of impaired absorption in these groups
- Onychomycosis (toenails with or without fingernail involvement)	200 mg o.d.	3 months	

For skin, vulvovaginal and oropharyngeal infections, optimal clinical and mycological effects are reached 1 - 4 weeks after cessation of treatment and for nail infections, 6 – 9 months after the cessation of treatment. This is because elimination of itraconazole from skin, nails and mucous membranes is slower than from plasma.

The length of treatment for systemic fungal infections should be dictated by the mycological and clinicalresponse to therapy:

INDICATIONS	**DOSE[1]**	**AVERAGE DURATION**	**REMARKS**
Aspergillosis	200 mg o.d.	2-5 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease
Candidiasis	100-200 mg o.d.	3 weeks-7months	
Non-meningeal cryptococcosis	200 mg o.d.	10 weeks	
Cryptococcal meningitis	200 mg b.i.d.	2 months – 6 months	

Histoplasmosis	200 mg o.d. 200 mg b.i.d.	8 months	
Maintenance in AIDS	200 mg o.d.		See note on impaired absorption below
Prophylaxis in neutropenia	200 mg o.d.		

[1] The duration of treatment should be adjusted depending on the clinical response. Impaired absorption inAIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. In such cases, blood level monitoring and if necessary, an increase in itraconazole dose to 200 mg twice daily, is indicated.

Special patient groups

Patients with impaired gastrointestinal motility

When treating patients with severe fungal infections or in the prophylaxis of fungal infections in patients with impaired gastrointestinal motility, pateints should be carefully monitored and, if available, therapeutic drug monitoring should be considered.

Paediatric population

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

Elderly patients

Clinical data on the use of itraconazole capsules in elderly patients are limited. It is advised to use itraconazole capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be takeninto consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and ofconcomitant disease or other drug therapy.

Patients with hepatic impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Cautionshould be exercised when this drug is administered in this patient population.

Patients with renal impairment

Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposureof itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised whenthis drug is administered in this patient population and adjusting the dose may be considered.

Method of administration

Itraconazole capsules is for oral administration and must be taken immediately after a meal for maximalabsorption.

Capsules must be swallowed whole with a small amount of water.

[1] We have recieved a few complaints from UK pharmacists stating that q.d. is confusing as on a prescription q.d.s. is four times a day, and once daily should be o.d. Therefore, to avoid incorrect dosagebeing given, we propose to change these abbreviations. b.i.d. means twice a day.

4.3 Contraindications

Itraconazole capsules are contraindicated in patients with known hypersensitivity to itraconazole or to anyof the excipients.

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

- Itraconazole capsules should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment oflife-threatening or other serious infections .

- Itraconazole capsules must not be used during pregnancy (except for life-threatening cases).

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

4.4 Special warnings and precautions for use

- Cross-hypersensitivity

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

- Cardiac effects

- In a healthy volunteer study with itraconazole IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. The clinical relevance of these findings to the oral formulations is unknown.

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

- Itraconazole should not be used in patients with congestive heart failure or with a history of

congestive heart failure unless the benefit clearly outweighs the risk. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g., total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, itraconazole should be discontinued.

- Calcium channel blockers can have negative inotropic effects which may be additive to those ofitraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of congestive heart failure.

- Hepatic effects

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

- 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 treatment with itraconazole capsules 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.

- Reduced gastric acidity

- Absorption of itraconazole from itraconazole capsules is impaired when gastric acidity is reduced. In patients with reduced gastric acidity, whether from disease (e.g. patients with

achlorhydria) or from concomitant medication (e.g. patients taking drugs that reduce gastric acidity), it is advisableto administer itraconazole capsules with a cola beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary.

- Paediatric population

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

- Use in elderly

- Clinical data on the use of itraconazole capsules in elderly patients is limited. It is advised to use Itraconazole capsules in these patients only if it is determined that the potential benefit outweighsthe 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, orcardiac function, and of concomitant disease or other drug therapy.

- Renal impairment

- Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose maybe considered.

- Hearing Loss

- Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated . The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

- Immunocompromised patients

- In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), theoral bioavailability of itraconazole capsules may be decreased.

- Patients with immediately life-threatening systemic fungal infections

- Due to the pharmacokinetic properties , itraconazole capsules are not recommended for initiationof treatment in patients with immediately life-threatening systemic fungal infections.

- Patients with AIDS

- In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal and non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

- Neuropathy

- If neuropathy occurs that may be attributable to itraconazole capsules, the treatment should be discontinued.

- Disorders of Carbohydrate Metabolism

- This drug contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose- galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

- Cross-resistance

- In systemic candidosis, if fluconazole-resistant strains of Candida species are suspected, it cannotbe assumed that these are sensitive to itraconazole, hence their sensitivity should be tested beforethe start of itraconazole therapy.

- Interchangeability

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

- Interaction potential

- Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death. Drugs that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole..

4.5 Interaction with other medicinal products and other forms of interaction

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

<u>Drugs that may decrease itraconazole plasma concentrations</u>

Drugs that reduce the gastric acidity (e.g. acid neutralising medicines such as aluminum hydroxide, or acid secretion suppressors such as H2-receptor antagonists and proton pump inhibitors) impair the absorption of itraconazole from itraconazole capsules . It is recommended that these drugs be used with caution whencoadministered with itraconazole capsules:

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

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

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

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

- Antibacterials: isoniazid, rifabutin (see also under Drugs that may have their plasma concentrationsincreased by itraconazole), rifampicin.

- Anticonvulsants: carbamazepine, (see also under Drugs that may have their plasma concentrationsincreased by itraconazole), phenobarbital, phenytoin.

- Antivirals: efavirenz, nevirapine.

- Herbal medicines : Hypericum perforatum (St John's Wort).

Therefore, administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. Itis 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 coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

<u>Drugs that may increase itraconazole plasma concentrations</u>

Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole.Examples include:
- Antibacterials: ciprofloxacin, clarithromycin, erythromycin,

- Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir (see also under Drugsthat 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 coadministered with itraconazole capsules.

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

<u>Drugs that may have their plasma concentrations increased by itraconazole</u>

Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of drugs metabolised by CYP3A4 and can inhibit the drug transport by P-glycoprotein, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are

administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. CYP3A4-metabolised 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.

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 beeven more gradual. This is particularly important when initiating therapy with drugs whose metabolism isaffected by itraconazole.

The interacting drugs are categorised as follows:

- 'Contraindicated': Under no circumstances is the drug to be coadministered with itraconazole, and up totwo 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 coadministration 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 coadministered with itraconazole.

Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting 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 drugclass with advice regarding coadministration with itraconazole:

Drug class	**Contrindicated**	**Not Recommended**	**Use with caution**
Alpha blockers		Tamsulosin	
Analgesics	Levacetylmethadol (levomethadyl), methadone	Fentanyl	Alfentanil, buprenorphine IV and sublingual, oxycodone, sufentanil
Antiarrhthmics	Disopyramide, dofetilide, dronedarone, quinidine		Digoxin
Antibacterials	Telithoromycin, in subjects with severe renal impairment or severe	Rifabutin[a]	Telithromycin

	hepatic impairment		
Anticoagulants and antiplatelet drugs	Dabigatran, ticagrelor	Apixaban, rivaroxaban	Coumarins, cilostazol
Anticonvulsivants		carbamazepinea	
Antidiabetics			Repaglinide, saxagliptin
Antihelmintics and antiprotozoals	Halofantrine		Praziquantel
Antihistamines	Astemizole, mizolastine, terfenadine	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, lapatinib, ponatanib, trimetrexate, vinca alkaloids
Antipsychotics, anxiolytics and hypnotics	Lurasidone, oral midazolam, pimozide, quetipine, sertindole, triazolam		Alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, ramelteon, risperidone
Antivirals		Simeprevir	Maraviroc, indinavirb, ritonavirb, saquinavir
Beta blockers			nadolol

Calcium cannel blockers	Bepridil, felodipine, lercanidipine, nisoldipine		Other dihydropyridines, including verapamil
Cardiovascular drugs, miscellaneous	Alikisiren, ivabradine, ranolazine	Sildenafil, for the treatment of pulmonary hypertension	Bosentan, riociguat
Diuretics	Eplerenone		
Gastrointestinal drugs	Cisapride, domperidone		Aprepitant
Immunosuppresants		Ciclesonide, everolimus, temsirolimus	Budesonide, ciclosporin, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as
			sirolimus), tacrolimus
Lipid regulating drugs	Atorvastatin, lovastatin, simvastatin		
Respiratory drugs		Salmeterol	
SSRIs, Tricyclics and Related antidepressants			Reboxetine
Urological drugs	Darifenacin, fesoterodine, in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment, solifenacin, in subjects with severe renal impairment or moderate to severe hepatic impairment		Fesoterodine, imidafenacin, oxybutynin, sildenafil, for the treatment of erectile dysfunction, solifenacin, tadalafil, tolterodine

Other	Colchicine, in subjects with renal or hepatic impairment	Colchicine, conivaptan	Alitretinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan

[a] See also under Drugs that may decrease itraconazole plasma concentrations [b] See also under Drugs that may increase itraconazole plasma concentrations Drugs that may have their plasma concentrations decreased by itraconazole

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Itraconazole 100mg Capsules, hard must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see section 4.3).

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

There is limited information on the use of itraconazole during pregnancy. During post-marketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiplemalformations. A causal relationship with itraconazole has not been established.

Epidemiological data on exposure to itraconazole during the first trimester of pregnancy – mostly in patients receiving short-term treatment for vulvovaginal candidosis – did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.

Women of childbearing potential

Women of childbearing potential taking Itraconazole 100mg Capsules, hard should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end ofItraconazole 100mg Capsules, hard therapy.

Breast-feeding

A very small amount of itraconazole is excreted in human milk.

The expected benefits of itraconazole capsules therapy should therefore be weighed against the potentialrisk of breast-feeding. In case of doubt, the patient should not breast-feed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss , which may occur in some instances, must be taken into account

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The ADRs in the table below were derived from open-label and double-blind clinical trials with itraconazole capsules involving 8499 patients in the treatment of dermatomycoses or onychomycosis, andfrom spontaneous reportingThe table below presents adverse drug reactions by System Organ Class.
Within each System Organ Class, the adverse drug reactions are presented by incidence, using thefollowing 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	
Infections and infestations	
Uncommon	Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and lymphatic system disorders	
Rare	Leukopenia
Immune system disorders	
Uncommon	Hypersensitivity*
Rare	Anaphylactic Reaction, Angioneurotic Oedema, Serum Sickness
Metabolism and nutrition disorders	
Rare	Hypertriglyceridemia
Nervous system disorders	
Common	Headache,

Rare	Hypoaesthesia, Paraesthesia, Dysgeusia
Eye disorders	
Rare	Visual Disturbance (including diplopia and blurred vision)
Ear and labyrinth disorder	
Rare	Tinnitus, Transient or permanent Hearing Loss*
Cardiac disorders	
Rare	Congestive Heart Failure*
Respiratory, thoracic and mediastinal disorders	
Rare	Dyspnoea
Gastrointestinal disorders	
Common	Abdominal Pain, Nausea
Uncommon	Vomiting, Diarrhoea, Constipation, Dyspepsia, Flatulence
Rare	Pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic function abnormal,
Rare	Serious hepatotoxicity (including some cases of fatal acute liver failure)*, Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, Rash, Pruritus
Rare	Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, Acute generalised exhanthematous pustulosis, Erythema Multiforme, Exfoliative Dermatitis, Leukocytoclastic Vasculitis, Alopecia, Photosensitivity
Renal and urinary disorders	
Rare	Pollakiuria
Reproductive system and breast disorders	
Uncommon	Menstrual Disorders
Rare	Erectile Dysfunction
General disorders and administration site conditions	
Rare	Oedema
Investigations	
Rare	Blood creatine phosphokinase increased

* see section 4.4.

Description of selected adverse reactions

The following is a list of ADRs associated with itraconazole that have been reported in clinical

trials of itraconazole oral solution and intraconazole I.V., excluding the ADR term "Injection site inflammation",which is specific to the injection route of administration.

Blood and lymphatic system disorders: Granulocytopenia, Thrombocytopenia

Immune system disorders: Anaphylactoid reaction

Metabolism and nutrition disorders: Hyperglycaemia, Hyperkalaemia, Hypokalaemia, Hypomagnesaemia

Psychiatric disorders: Confusional state

Nervous system disorders: Peripheral neuropathy (see section 4.4)*, Dizziness, Somnolence, Tremor

Cardiac disorders: Cardiac failure, Left ventricular failure, Tachycardia

Vascular disorders: Hypertension, Hypotension

Respiratory, thoracic and mediastinal disorders: Pulmonary oedema, Dysphonia, Cough

Gastrointestinal disorders: Gastrointestinal disorder

Hepatobiliary disorders: Hepatic failure (see section 4.4)*, Hepatitis, Jaundice **Skin and subcutaneous tissue disorders:** Rash erythematous, Hyperhidrosis **Musculoskeletal and connective tissue disorders:** Myalgia, Arthralgia
Renal and urinary disorders: Renal impairment, Urinary incontinence

General disorders and administration site conditions: Generalised oedema, Face oedema, Chest pain,Pyrexia, Pain, Fatigue, Chills

Investigations: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Blood urea increased, Gamma- glutamyltransferase increased, Hepatic enzyme increased, Urine analysis abnormal

Paediatric population

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

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

4.9 Overdose

Symptoms and signs

In general, adverse events reported with overdose have been consistent with those reported for itraconazole use.

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 hemodialysis. 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 ofmembrane synthesis by fungi.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic relationship for itraconazole, and for triazoles in general, ispoorly 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 $\leq$0.125

µg/mL, susceptible, dose- dependent 0.25-0.5 mg/mL and resistant ≥1 µg/mL. Interpretive breakpoints have not been established forthe filamentous fungi.

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 agentin 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]
Penicillium marneffei[1]
Pseudallescheria boydii
Sporothrix schenckii
Trichophyton spp.
Trichosporon spp.
Species for which acquired resistance may be a problem
Candida glabrata[3]
Candida krusei
Candida tropicalis[3]

Inherently resistant organisms
Absidia spp.
Fusarium spp.
Mucor spp.
Rhizomucor spp.
Rhizopus spp.
Scedosporium proliferans
Scopulariopsis spp.

[1] These organisms may be encountered in patients who have returned from travel outside Europe.

[2] Itraconazole-resistant strains of Aspergillus fumigatus have been reported.

[3] Natural intermediate susceptibility.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics.

Peak plasma concentrations are reached within 2 to 5 hours after oral administration. As a consequence ofnon-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with Cmax values of 0.5 μg/ml, 1.1 μg/ml and
2.0 μg/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single doseand increases to 34 to 42 hours with repeated dosing.

Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Absorption

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately aftera full meal.

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases . Absorption of itraconazole under fasted conditions in these subjects is increased when itraconazole capsules are administered with an acidic beverage (such as a non-diet cola). When itraconazole capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H2-receptor antagonist,itraconazole absorption was

comparable to that observed when itraconazole capsules were administered alone.

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the samedose of drug is given.

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, is up to four times higher than in plasma. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

Biotransformation

Itraconazole is extensively metabolized by the liver into a large number of metabolites. In vitro studies, CYP 3A4 is the major enzyme that is 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 the hydroxy-itraconazole are about twice those of itraconazole. .

Elimination

Itraconazole is excreted as inactive metabolites in urine (35%) and faeces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxyl-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, fecal excretion ofunchanged drug varies between 3 – 18% of the dose.

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 ibn AUC, was similar in cirrhotic patients and in healthy subjects.

Data are not available in cirrhotic patients during long-term use of itraconazole. .

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

conductedin 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 noeffect on the half-life or clearance of itraconazole or hydroxy-itraconazole.

Paediatric Population

Limited pharmacokinetic data are available on the use of itraconazole in the paediatric population. Clinicalpharmacokinetic studies in children and adolescents aged between 5 months and 17 years were performed with itraconazole capsules, oral solution or intravenous formulation. Individual doses with the capsule andoral solution formulation ranged from 1.5 to 12.5 mg/kg/day, given as once-daily or twice-daily administration. The intravenous formulation was given either as a 2.5 mg/kg single infusion, or a 2.5 mg/kg infusion given once daily or twice daily. For the same daily dose, twice daily dosing compared to single daily dosing yielded peak and trough concentrations comparable to adult single daily dosing. No significant age dependence was observed for itraconazole AUC and total body clearance, while weak associations between age and itraconazole distribution volume, Cmax and terminal elimination rate were noted. Itraconazole apparent clearance and distribution volume seemed to be related to weight.

5.3 Preclinical safety data

Nonclinical data on itraconazole revealed no indications for gene toxicity, primary carcinogenicity or impairment of fertility. At high doses, effects were observed in the adrenal cortex, liver and the mononuclear phagocyte system but appear to have a low relevance for the proposed clinical use. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats and mice at high doses. A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed

6. Pharmaceutical particulars

6.1 List of excipients
EHG Size "0" Blue / white

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store at temperature not exceeding 30ºC. Protect from light.

6.5 Nature and contents of container
10x1x10 Capsules in Alu-alu blister packed in a printed carton along with leaflet.

6.6 Special precautions for disposal and other handling
No special requirements.