PRODUCT MONOGRAPH

Pr ODAN ITRACONAZOLE

Itraconazole Oral Solution, BP

10 mg / mL

Antifungal Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Solution 10 mg / mL	hydroxypropyl-ß-cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour, sodium saccharin, sodium hydroxide and purified water.

INDICATIONS AND CLINICAL USE

ODAN ITRACONAZOLE (itraconazole) oral solution 10 mg/mL is indicated for the treatment of oral and/or esophageal candidiasis in adult HIV-positive or other immunocompromised patients.

ODAN ITRACONAZOLE oral solution as treatment for oral and/or esophageal candidiasis was not investigated in neutropenic patients. Due to the pharmacokinetic properties (see **DETAILED PHARMACOLOGY, Human Pharmacokinetics**), ODAN ITRACONAZOLE oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis.

Note: Itraconazole oral solution and itraconazole capsules should not be used interchangeably.

Geriatrics (> 65 years of age):
Clinical data on the use of itraconazole oral solution in elderly patients are limited. It is advised to use ODAN ITRACONAZOLE oral solution in these patients only if it is determined that the potential benefit outweighs the potential risks (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Pediatrics (< 18 years of age):
The efficacy and safety of itraconazole oral solution have not been established in pediatric patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

CONTRAINDICATIONS

- ODAN 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 Table 1, Calcium Channel Blockers; **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions** and **Cardiovascular,** Use in Patients with Underlying Cardiac Disease; **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

- Coadministration with itraconazole oral solution, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, causes elevated plasma concentrations of drugs metabolized by this pathway which may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. Drugs that are contraindicated in combination with itraconazole are listed in Table 1 (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions** and **DRUG INTERACTIONS, Serious Drug Interactions; Drug-Drug Interactions, Table 3**).

Table 1: Drugs that are contraindicated with Odan Itraconazole oral solution

Drug Class	Drugs within Class that are Contraindicated with Odan Itraconazole oral solution
Analgesics	methadone
Antiarrhythmics	disopyramide, dronedarone, quinidine
Anticoagulants and Antiplatelet Drugs	ticagrelor
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, eletriptan
Antineoplastics	irinotecan
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, pimozide, triazolam
Antivirals	asunaprevir (boosted)
Calcium Channel Blockers	felodipine
Cardiovascular Drugs,	ivabradine, ranolazine
Diuretics	eplerenone
Gastrointestinal Drugs	domperidone, naloxegol
Lipid Regulating Drugs	lomitapide, lovastatin, simvastatin
Urologic Drugs	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.
Miscellaneous Drugs and Other Substances	colchicine, in subjects with renal or hepatic impairment, eliglustat.

- ODAN ITRACONAZOLE oral solution is contraindicated in patients with a known hypersensitivity to itraconazole or its excipients. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

- There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing ODAN ITRACONAZOLE oral solution to patients with hypersensitivity to other azoles.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Congestive Heart Failure: ODAN ITRACONAZOLE (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.** If signs or symptoms of congestive heart failure occur during administration of ODAN ITRACONAZOLE oral solution, discontinue administration. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen (see **CONTRAINDICATIONS,** Table 1**,** Calcium Channel Blockers**; WARNINGS AND PRECAUTIONS**, **Cardiovascular,** Use in Patients with Underlying Cardiac Disease; **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
- **Drug Interactions: Coadministration of a number of CYP3A4 substrates with ODAN ITRACONAZOLE oral solution is contraindicated.** Coadministration with itraconazole , a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, causes increased plasma concentrations of drugs metabolized by this pathway which may increase or prolong both therapeutic and adverse effects to such an extent that a potentially 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. Drugs that are contraindicated are listed in Table 1 (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Serious Drug Interactions and Drug-Drug Interactions, Table 3**).
- **Liver Toxicity:** Itraconazole oral solution has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment. It is advisable to monitor liver function. If clinical signs or symptoms develop that are consistent with liver disease, such as anorexia, nausea, vomiting, jaundice, fatigue, abdominal pain, dark urine, or pale stools, treatment should be discontinued and liver function testing performed. Continued use of ODAN ITRACONAZOLE oral solution or reinstitution of treatment with ODAN ITRACONAZOLE oral solution is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **ADVERSE REACTIONS**).

General

Itraconazole oral solution and itraconazole capsules should not be used interchangeably. **ODAN ITRACONAZOLE** oral solution is indicated only for the treatment of oropharyngeal and/or esophageal candidiasis. The efficacy of itraconazole oral solution for other indications is unknown. The two dosage forms have different absorption profiles (see **DETAILED PHARMACOLOGY, Human Pharmacokinetics**).

In patients receiving continuous treatment of more than one month and in patients developing symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine, it is advisable to monitor liver function. If tests are abnormal, treatment should be terminated.

In systemic candidosis, if fluconazole-resistant strains of *Candida* species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence it is recommended to have their sensitivity tested before the start of itraconazole therapy (see **MICROBIOLOGY, Resistance and Cross-Resistance**).

Carcinogenesis and Mutagenesis

ODAN ITRACONAZOLE oral solution contains the excipient hydroxypropyl-β-cyclodextrin, which produced adenocarcinomas in the large intestine and exocrine pancreas in a rat carcinogenicity study, but not in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown.

See **TOXICOLOGY, Carcinogenicity** for discussion on itraconazole animal data.

Cardiovascular

Cardiac Dysrhythmias

Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as methadone, pimozide or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Serious Drug Interactions** and **Drug-Drug Interactions, Table 3**).

Use in Patients with Underlying Cardiac Disease

Itraconazole has been associated with reports of CHF. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg than among those receiving lower total daily doses. This suggests that the risk of heart failure might increase with the total daily dose of itraconazole.

ODAN ITRACONAZOLE oral solution should not be used in patients with evidence of ventricular dysfunction such as CHF or a history of CHF unless the benefit clearly outweighs the risk.

The benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g., total daily dose), and the 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; renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, treated with caution, and monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, ODAN ITRACONAZOLE oral solution should be discontinued (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions** and **DRUG INTERACTIONS**).

Itraconazole has been shown to have a negative inotropic effect. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study (n=8) of itraconazole for injection, a transient asymptomatic decrease of the left ventricular ejection fraction was observed using gated SPECT imaging; this resolved before the next infusion, 12 hours later.

Calcium channel blockers can have negative inotropic effects which may be additive to those of

itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when coadministering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of ODAN ITRACONAZOLE with felodipine is contraindicated.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Ear/Nose/Throat

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 **CONTRAINDICATIONS**). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Hepatic/Biliary/Pancreatic

Hepatic Effects

Rare cases of serious hepatotoxicity (including liver failure and death) have been observed with itraconazole treatment. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition and some of these cases developed within the first week of treatment.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with ODAN ITRACONAZOLE oral solution is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. Liver function monitoring should be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications and should be considered in all patients receiving ODAN ITRACONAZOLE oral solution.

Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction. Such signs and symptoms include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, abdominal pain, dark urine or pale stools (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions** box; **General**, and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Itraconazole binds extensively to plasma proteins.

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. In a clinical trial in cirrhotic patients, the mean terminal half-life of itraconazole was increased by 131% and its mean C_{max} decreased by 47%. 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 (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

Neurologic
If neuropathy occurs that may be attributable to ODAN ITRACONAZOLE oral solution, the treatment should be discontinued.

Renal
Use in Patients with Renal Insufficiency
Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency**).

In a few patients, hypokalemia has been reported. Consequently serum potassium should be monitored in patients at risk during high-dose itraconazole therapy.

Itraconazole cannot be removed by hemodialysis.

Effects on Ability to Drive and Use Machines
Adverse reactions such as dizziness, visual disturbances and hearing loss have been reported while taking itraconazole. These adverse reactions may impair the ability to drive a vehicle and operate machinery (see **ADVERSE REACTIONS**, **Post-Market Adverse Drug Reactions**).

Special Populations

Pregnant Women: ODAN 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 fetus. Itraconazole has been shown to produce teratogenic effects (major skeletal and secondary soft tissue defects) when administered at high doses (40 mg/kg/day, 5 times the maximum recommended human dose (MRHD) or higher) to pregnant rats. When administered to pregnant mice at high doses (80 mg/kg/day, 10 times MRHD or higher), itraconazole has been shown to produce encephaloceles and/or macroglossia.

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 multiple malformations. A causal relationship with itraconazole oral solution has not been established.

Pregnancy should be avoided in women using itraconazole and for 2 months following end of treatment. In women of child bearing potential, a reliable method of barrier contraception must always be used in combination with other methods of contraception e.g. oral or other hormonal contraceptives (see **DRUG INTERACTIONS**).

Nursing Women: Itraconazole is excreted in human milk; therefore, the patient should be advised to discontinue nursing while taking ODAN ITRACONAZOLE oral solution.

Pediatrics (< 18 years of age):
The efficacy and safety of itraconazole oral solution have not been established in pediatric patients. ODAN ITRACONAZOLE oral solution should not be used in pediatric patients unless the potential benefit outweighs the potential risks. Clinical data on the use of itraconazole oral solution in pediatric patients are limited. A pharmacokinetic study was conducted with itraconazole oral solution in 26 pediatric patients, ages 6 months to 12 years, requiring systemic antifungal treatment. Itraconazole was dosed at 5 mg/kg once daily for 2 weeks and no serious unexpected adverse events were reported (see **DETAILED PHARMACOLOGY, Human Pharmacokinetics**).

Toxicological studies have shown that itraconazole, when administered to rats, can produce bone toxicity. While no such toxicity has been reported in adult patients, the long-term effect of itraconazole in children is unknown (see **TOXICOLOGY**).

Geriatrics (> 65 years of age): Clinical data on the use of itraconazole oral solution in elderly patients are limited. It is advised to use ODAN 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 concomitant disease or other drug therapy.

Cystic Fibrosis:
In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady-state dosing of itraconazole oral solution using 2.5 mg/kg b.i.d. Steady-state concentrations of > 250 ng/mL were achieved in approximately 50% of subjects greater than 16 years of age, but in none of the patients less than 16 years of age. If a patient does not respond to ODAN ITRACONAZOLE oral solution, consideration should be given to switching to alternative therapy.

Use in Acquired Immunodeficiency Syndrome (AIDS) and Neutropenic Patients:
Studies with itraconazole capsules in neutropenic and AIDS patients have indicated that itraconazole plasma concentrations are lower than those in healthy subjects (particularly in those patients who are achlorhydric). However, the bioavailability of itraconazole oral solution, when tested in AIDS patients, was found satisfactory and not altered by the stage of HIV infection.

The results from a study in which 8 HIV-infected individuals were treated with zidovudine, 8 ± 0.4 mg/kg/day with or without itraconazole capsules 100 mg b.i.d., showed that the pharmacokinetics of zidovudine were not affected during concomitant administration of itraconazole capsules.

Monitoring and Laboratory Tests
Due to the presence of an active metabolite, hydroxy-itraconazole, plasma levels monitored by bioassay will yield plasma levels roughly three times higher than that obtained by high-pressure liquid chromatography (HPLC), unless solvent conditions for the HPLC assay are adjusted to allow simultaneous detection of both the parent drug and the metabolite.

Liver function monitoring should be done in patients with pre-existing hepatic abnormalities, or those who have experienced liver toxicity with other medications and should also be considered in all patients receiving treatment with ODAN ITRACONAZOLE oral solution. Hypokalemia

has been reported in a few patients. Therefore, serum potassium should be monitored in patients at risk during high-dose itraconazole therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Itraconazole has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, treatment should be discontinued and liver function testing performed. Before consideration is given to reinstituting therapy, the risks and benefits of itraconazole use should be reassessed (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Itraconazole Oral Solution

The adverse event profile was analyzed for 889 HIV-positive and other immunocompromised patients receiving itraconazole oral solution for the treatment of oral and esophageal candidiasis. The most frequently reported adverse events were of gastrointestinal origin. The total observed incidence of adverse events that are possibly or directly drug related, during treatment or within 14 days post-treatment for itraconazole oral solution is 18.2%. A listing of adverse events reported with a frequency ≥ 1% for itraconazole in all worldwide studies of oropharyngeal and esophageal candidiasis is presented in Table 2.

Table 2: Adverse experience incidence ≥1.0% in worldwide trials of oropharyngeal and esophageal candidiasis, by body system

Body System/adverse event	itraconazole n=889
Gastrointestinal system disorder	12.3%
Nausea	5.3%
Diarrhea	4.5%
Vomiting	3.4%
Abdominal pain	2.5%
Skin and appendages disorders	2.4%
Rash	1.3%
Central and peripheral nervous system	1.7%
Headache	1.1%
Liver and biliary system disorders	1.3%
Special senses	1.1%
Taste perversion	1.0%
Body as a whole	1.0%

Post-Market Adverse Drug Reactions

Worldwide post-marketing experiences with the use of itraconazole (across all three itraconazole formulations: itraconazole capsules, itraconazole oral solution and itraconazole IV) include the adverse events listed below.

Infections and Infestations: sinusitis, upper respiratory tract infection, rhinitis
Blood and lymphatic system disorders: granulocytopenia, leukopenia, neutropenia, thrombocytopenia
Immune system disorders: serum sickness, angioneurotic edema, anaphylactic, anaphylactoid and allergic reactions, hypersensitivity
Metabolism and nutrition disorders: hyperglycemia, hypertriglyceridemia, hypokalemia, hypomagnesemia
Psychiatric disorders: confusional state
Nervous system disorders: peripheral neuropathy, paresthesia, hypoesthesia, headache, dizziness, somnolence, tremor
Eye disorders: visual disturbances, including vision blurred and diplopia
Ear and labyrinth disorders: tinnitus, transient or permanent hearing loss
Cardiac disorders: congestive heart failure, cardiac failure, left ventricular failure, tachycardia
Vascular disorders: hypertension, hypotension
Respiratory, thoracic and mediastinal disorders: pulmonary edema, dyspnea, dysphonia
Gastrointestinal disorders: pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhea, constipation, dysgeusia, gastrointestinal disorder, flatulence
Hepatobiliary disorders: serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes, hepatic function abnormal, hepatic failure, hyperbilirubinemia, jaundice
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus, rash erythematous, hyperhidrosis
Investigations: blood creatine phosphokinase increased, 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
Musculoskeletal and connective tissue disorders: myalgia, arthralgia
Renal and urinary disorders: pollakiuria, urinary incontinence, renal impairment
Reproductive system and breast disorders: menstrual disorders, erectile dysfunction
General disorders and administration site conditions: edema, pyrexia, generalized edema, face edema, chest pain, pain, fatigue, chills

DRUG INTERACTIONS

Serious Drug Interactions

ODAN ITRACONAZOLE oral solution is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. 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 a potentially serious situation may occur. Coadministration of a number of CYP3A4 substrates is contraindicated with ODAN ITRACONAZOLE oral solution. 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.
Drugs that are contraindicated with ODAN ITRACONAZOLE oral solution are listed below:

methadone, disopyramide, dronedarone, quinidine, ticagrelor, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, irinotecan, lurasidone, pimozide, triazolam, asunaprevir (boosted), felodipine, ivabradine, ranolazine, eplerenone, domperidone, naloxegol, lomitapide, lovastatin, simvastatin, 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), eletriptan, colchicine (in subjects with renal or hepatic impairment), eliglustat.

See **CONTRAINDICATIONS, Table 1; WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions**.

Overview

Itraconazole is a drug with a high interaction potential. The various types of interaction and associated general recommendations are described below. In addition, Table 3 provides listing examples of drugs that may interact with itraconazole, organized per drug family for easy reference. This list of examples is not comprehensive and therefore the Product Monograph (PM) of each drug that is coadministered with itraconazole should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to coadministration.

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Coadministration of itraconazole with moderate or potent CYP3A4 inducers may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be reduced. Coadministration with moderate or potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole, which may result in increased or prolonged pharmacologic effects of itraconazole.

Itraconazole and its major metabolite, hydroxy-itraconazole are potent CYP3A4 inhibitors. Itraconazole is an inhibitor of the drug transporters P-glycoprotein and breast cancer resistance protein (BCRP). Itraconazole can inhibit the metabolism of drugs metabolized by CYP3A4 and can inhibit the drug transport by P-glycoprotein and/or BCRP, 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. For some drugs, coadministration with itraconazole may result in decreased plasma concentrations of the drug or of the active moiety of the drug. This may result in reduced efficacy of the drug.

Following cessation of medical treatment with itraconazole, plasma concentrations decrease below the detection limit 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 plasma concentrations decline slower. This is particularly important for consideration when initiating therapy with drugs whose metabolism is affected by itraconazole.

The following general recommendations apply, unless stated differently in Table 3.

- '**CONTRAINDICATED**': Under no circumstances is the drug to be coadministered with itraconazole. This applies to:
    - CYP3A4 substrates for which increased plasma concentrations may increase or prolong therapeutic and/or adverse effects to such an extent that a potentially serious situation may occur (see **CONTRAINDICATIONS**).
- '**NOT RECOMMENDED**': It is recommended that the use of the drug be avoided, unless the benefits outweigh the potentially increased risks. If coadministration cannot be avoided, clinical monitoring is recommended, and the dosage of itraconazole and/or the coadministered drug adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Moderate or potent CYP3A4 inducers: not recommended from 2 weeks before and during treatment with itraconazole
    - CYP3A4/P-gp/BCRP substrates for which increased or decreased plasma concentrations result in significant risk: not recommended during and up to 2 weeks after treatment with itraconazole.
- '**USE WITH CAUTION**': Careful monitoring is recommended when the drug is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely and the dosage of itraconazole and/or the coadministered drug adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Moderate or potent inhibitors of CYP3A4
    - CYP3A4/P-gp/BCRP substrates for which increased or decreased plasma concentrations result in a clinically relevant risk

Examples of interacting drugs are listed in Table 3 below. The drugs listed in this table are based on either drug interaction studies or case reports, or potential interactions based on the mechanism of interaction. This list is not all-inclusive.

Drug-Drug Interactions

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Alpha Blockers		

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Alfuzosin Silodosin Tamsulosin	Alfuzosin C_{max} (↑↑), AUC (↑↑)[a] Silodosin C_{max} (↑↑), AUC (↑↑)[a] Tamsulosin C_{max} (↑↑), AUC (↑↑)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of alfuzosin/silodosin/ tamsulosin-related adverse reactions[c].
Analgesics		
Alfentanil Buprenorphine (IV and sublingual) Oxycodone Sufentanil	Alfentanil AUC (↑↑ to ↑↑↑↑)a Buprenorphine C_{max} (↑↑), AUC (↑↑)a Oxycodone C_{max} ↑, AUC ↑↑ Sufentanil conc increase (extent unknown)[a,b]	**USE WITH CAUTION**, monitor for adverse reactions related to the analgesic[c] dose reduction of alfentanil/buprenorphine/ oxycodone/sufentanil may be necessary.
Fentanyl	Fentanyl IV AUC (↑↑)[a] Fentanyl other form. conc increase (extent unknown)[a,b]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of fentanyl-related adverse reactions[c].
Methadone	(R)-methadone C_{max} (↑), AUC (↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of methadone-related adverse reactions, such as potentially life-threatening respiratory depression, QT prolongation and TdP.
Anti-arrhythmics		
Digoxin	Digoxin C_{max} ↑, AUC ↑	**USE WITH CAUTION**, monitor for digoxin adverse reactions, dose reduction of digoxin may be necessary[c].
Disopyramide	Disopyramide conc increase (↑↑)[a,b]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of disopyramide-related adverse reactions, such as serious arrhythmias including TdP.
Dronedarone	Dronedarone C_{max} (↑↑↑), AUC (↑↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of dronedarone-related adverse reactions, such as QT prolongation and cardiovascular death.
Quinidine	Quinidine C_{max} ↑, AUC ↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of quinidine-related adverse reactions, such as QT prolongation, TdP, hypotension, confusion and delirium.
Antibacterials		
Ciprofloxacin Erythromycin	Itraconazole C_{max} ↑, AUC ↑	**USE WITH CAUTION**, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Clarithromycin	Clarithromycin conc increase (extent unknown)[a,b] Itraconazole C_{max} ↑, AUC ↑;	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or clarithromycin[c], dose reduction of itraconazole and/or clarithromycin may be necessary.
Isoniazid Rifampicin	Isoniazid: itraconazole conc. (↓↓↓)[a,b] Rifampicin: itraconazole AUC ↓↓↓	**NOT RECOMMENDED** from 2 weeks before and during treatment with itraconazole, Itraconazole efficacy may be reduced.
Rifabutin	Rifabutin conc. increase (extent unknown)[a,b] Itraconazole: C_{max} ↓↓, AUC ↓↓	**NOT RECOMMENDED** from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of rifabutin-related adverse reactions[c].
Anticoagulants and Antiplatelet Drugs		
Apixaban Rivaroxaban Vorapaxar	Apixaban C_{max} (↑), AUC (↑)[a] Rivaroxaban C_{max} (↑), AUC (↑ to ↑↑)[a] Vorapaxar C_{max} (↑), AUC (↑)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of apixaban/rivaroxaban/vorapaxar-related adverse reactions[c].
Coumarins (eg, warfarin) Cilostazol	Coumarins (eg, warfarin) conc increase (extent unknown)[a,b] Cilostazol C_{max} (↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for coumarins/cilostazol adverse reactions, dose reduction of coumarins/cilostazol may be necessary[c].
Dabigatran	Dabigatran C_{max} (↑↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for dabigatran adverse reactions, dose reduction of dabigatran may be necessary[c].
Ticagrelor	Ticagrelor C_{max} (↑↑), AUC (↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ticagrelor-related adverse reactions, such as bleeding.
Anticonvulsants		
Carbamazepine	Carbamazepine conc. (↑)[a,b] Itraconazole conc. (↓↓)[a,b]	**NOT RECOMMENDED** from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk for carbamazepine-related adverse reactions[c].
Phenobarbital Phenytoin	Phenobarbital: itraconazole conc. (↓↓↓)[a,b] Phenytoin: itraconazole AUC ↓↓↓	**NOT RECOMMENDED** from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Antidiabetics		

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Repaglinide Saxagliptin	Repaglinide C_{max} ↑, AUC ↑ Saxagliptin C_{max} (↑↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for repaglinide/saxagliptin adverse reactions, dose reduction of repaglinide/saxagliptin may be necessary[c].
Antihelminthics, antifungals and antiprotozoals		
Quinine	Quinine C_{max} ↔, AUC ↑	**USE WITH CAUTION**, monitor for quinine adverse reactions[c]. Refer to the Product Monograph (PM) for specific actions to be taken**.**
Praziquantel	Praziquantel C_{max} (↑↑), AUC (↑)[a]	**USE WITH CAUTION**, monitor for praziquantel adverse reactions, dose reduction of praziquantel may be necessary[c].
Antihistamines		
Bilastine Ebastine Rupatadine	Bilastine C_{max} (↑↑), AUC (↑)[a] Ebastine C_{max} ↑↑, AUC ↑↑↑ Rupatadine conc increase (↑↑↑↑)[a,b]	**USE WITH CAUTION**, monitor for bilastine/ebastine/rupatadine adverse reactions[c], dose reduction of bilastine/ebastine/rupatadine may be necessary.
Antimigraine Drugs		
Eletriptan	Eletriptan C_{max} (↑↑), AUC (↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Coadministration of eletriptan with itraconazole can elevate plasma eletriptan concentrations which could result in serious adverse events.
Ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine)	Ergot alkaloids conc increase (extent unknown)[a,b]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism.
Antineoplastics		
Bortezomib Brentuximab vedotin Busulfan Erlotinib Gefitinib Imatinib Ixabepilone Nintedanib Ponatinib Ruxolitinib Vandetanib	Bortezomib AUC (↑)[a] Brentuximab vedotin AUC (↑)[a] Busulfan C_{max} ↑, AUC ↑ Erlotinib C_{max} (↑↑), AUC (↑)[a] Gefitinib C_{max} ↑, AUC ↑ Imatinib C_{max} (↑), AUC (↑)[a] Ixabepilone C_{max} (↔), AUC (↑)[a] Nintedanib C_{max} (↑), AUC (↑)[a] Ponatinib C_{max} (↑), AUC (↑)[a] Ruxolitinib C_{max} (↑), AUC (↑)[a] Vandetanib C_{max} ↔, AUC ↑	**USE WITH CAUTION**, monitor for adverse reactions related to the antineoplastic drug[c], dose reduction of the antineoplastic drug may be necessary.
Idelalisib	Idelalisib C_{max} (↑), AUC (↑)[a] Itraconazole serum conc. increase (extent unknown)[a,b]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or idelalisib[c], dose reduction of itraconazole and/or idelalisib may be necessary.

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Axitinib Bosutinib Cabazitaxel Ceritinib Cobimetinib Crizotinib Dabrafenib Dasatinib Docetaxel Ibrutinib Lapatinib Nilotinib Olaparib Pazopanib Sunitinib Trabectedin Trastuzumab emtansine Vinca alkaloids	Axitinib C_{max} (↑), AUC (↑↑)[a] Bosutinib C_{max} (↑↑↑), AUC (↑↑↑)[a] Cabazitaxel C_{max} (↔), AUC (↔)[a] Ceritinib C_{max} (↑), AUC (↑↑)[a] Cobimetinib C_{max} ↑↑, AUC ↑↑↑ Crizotinib C_{max} (↑), AUC (↑↑)[a] Dabrafenib AUC (↑)[a] Dasatinib C_{max} (↑↑), AUC (↑↑)[a] Docetaxel AUC (↔ to ↑↑)[a] Ibrutinib C_{max} (↑↑↑↑), AUC (↑↑↑↑)[a] Lapatinib C_{max} (↑↑), AUC (↑↑)[a] Nilotinib C_{max} (↑), AUC (↑↑)[a] Olaparib C_{max} ↑, AUC ↑↑ Pazopanib C_{max} (↑), AUC (↑)[a] Sunitinib C_{max} (↑), AUC (↑)[a] Trabectedin C_{max} (↑), AUC (↑)[a] Trastuzumab emtasine conc increase (extent unknown)[a,b] Vinca alkaloid conc increase (extent unknown)[a,b]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the antineoplastic drug[c]. Additionally: For cabazitaxel, even though the change in pharmacokinetic parameters did not reach statistical significance in a low-dose drug interaction study with ketoconazole, a high variability in the results was observed. For ibrutinib, refer to the Product Monograph for specific actions to be taken.
Regorafenib	Regorafenib AUC (↓↓ by estimation of active moiety)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Regorafenib efficacy may be reduced.
Irinotecan	Irinotecan and its active metabolite conc increase (extent unknown)[a,b]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of irinotecan-related adverse reactions, such as potentially life-threatening myelosuppression and diarrhea.
Antipsychotics, Anxiolytics and Hypnotics		
Alprazolam Aripiprazole Brotizolam Buspirone Haloperidol Midazolam (iv) Perospirone Quetiapine Ramelteon Risperidone Zopliclone	Alprazolam C_{max} ↔, AUC ↑↑ Aripiprazole C_{max} ↑, AUC ↑ Brotizolam C_{max} ↔, AUC ↑↑ Buspirone C_{max} ↑↑↑↑, AUC ↑↑↑↑ Haloperidol C_{max} ↑, AUC ↑ Midazolam (iv) conc increase ↑↑[b] Perospirone C_{max} ↑↑↑, AUC ↑↑↑ Quetiapine C_{max} (↑↑), AUC (↑↑↑)[a] Ramelteon C_{max} (↑), AUC (↑)[a] Risperidone conc increase ↑[b] Zopiclone C_{max} ↑, AUC ↑	**USE WITH CAUTION**, monitor for adverse reactions related to the antipsychotic, anxiolytic or hypnotic drug[c], dose reduction of these drugs may be necessary.
Lurasidone	Lurasidone C_{max} (↑↑↑), AUC (↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of lurasidone-related adverse reactions, such as hypotension, circulatory collapse, severe extrapyramidal symptoms, seizures.

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Pimozide	Pimozide C_{max} (↑), AUC (↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of pimozide-related adverse reactions, such as cardiac arrhythmias, possibly associated with QT prolongation and TdP.
Triazolam	Triazolam C_{max} ↑ to ↑↑, AUC ↑↑ to ↑↑↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of triazolam-related adverse reactions, such as seizures, respiratory depression, angioedema, apnea and coma.
Antivirals		
Asunaprevir (boosted)	Asunaprevir C_{max} (↑↑↑), AUC (↑↑↑)[a]	**CONTRAINDICATED**, refer to the PM of the antiviral drug for specific actions to be taken.
Tenofovir disoproxil fumarate (TDF)	Tenofovir conc increase (extent unknown)[a,b]	**USE WITH CAUTION**, however, refer to the PM of the antiviral drug for specific actions to be taken.
Cobicistat	Cobicistat conc increase (extent unknown)[a,b] Itraconazole conc increase (extent unknown)[a,b]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole, dose reduction of itraconazole may be necessary.
Daclatasvir	Daclatasvir C_{max} (↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for daclatasvir adverse reactions[c], dose reduction of daclatasvir may be necessary.
Darunavir (boosted) Fosamprenavir (ritonavir- boosted) Telaprevir	Ritonavir-boosted darunavir: itraconazole C_{max} (↑↑), AUC (↑↑)[a] Ritonavir-boosted fosamprenavir: itraconazole C_{max} (↑), AUC (↑↑)[a] Telaprevir: itraconazole C_{max} (↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
Elvitegravir (boosted)	Elvitegravir C_{max} (↑), AUC (↑)[a] Itraconazole conc increase (extent unknown)[a,b]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or elvitegravir (ritonavir-boosted)[c]. Dose reduction of itraconazole may be necessary; refer to the elvitegravir PM for specific actions to be taken.
Efavirenz Nevirapine	Efavirenz: itraconazole C_{max} ↓, AUC ↓ Nevirapine: itraconazole C_{max} ↓, AUC ↓↓	**NOT RECOMMENDED** from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Elbasvir/Grazoprevir	Elbasvir C_{max} (↔), AUC (↑)[a] Grazoprevir C_{max} (↔), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for adverse reactions related to the co-administered drugs[c]. Refer to the elbasvir/grazoprevir PM for specific actions to be taken.

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Glecaprevir/Pibrentasvir	Glecaprevir C_{max} (↑↑), AUC (↑↑ to ↑↑↑)[a] Pibrentasvir C_{max} (↔ to ↑), AUC (↔ to ↑↑)[a]	**USE WITH CAUTION**, monitor for adverse reactions related to the co-administered drugs[c]. Refer to the glecaprevir/pibrentasvir PM for specific actions to be taken.
Indinavir	Itraconazole conc. ↑[b] Indinavir C_{max} ↔, AUC ↑	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or indinavir[c], dose reduction of itraconazole and/or indinavir may be necessary.
Maraviroc	Maraviroc C_{max} (↑↑), AUC (↑↑↑)[a]	**USE WITH CAUTION** monitor for adverse reactions[c]. Dose reduction of maraviroc may be necessary.
Ritonavir	Itraconazole C_{max} (↑), AUC (↑↑)[a] Ritonavir C_{max} (↔), AUC (↑)[a]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or ritonavir[c], Dose reduction of itraconazole may be necessary; refer to the ritonavir PM for specific actions to be taken.
Saquinavir	Saquinavir (unboosted) C_{max} ↑↑, AUC ↑↑↑ Itraconazole (with boosted saquinavir) C_{max} (↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or saquinavir[c], Dose reduction of itraconazole may be necessary; refer to the saquinavir PM for specific actions to be taken.
Simeprevir	Simeprevir C_{max} (↑↑), AUC (↑↑↑)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole.
Beta Blockers		
Nadolol	Nadolol C_{max} ↑↑, AUC ↑↑	**USE WITH CAUTION**, monitor for nadolol adverse reactions[c]. Dose reduction of nadolol may be necessary.
Calcium Channel Blockers		
Diltiazem	Diltiazem & Itraconazole conc increase (extent unknown)[a,b]	**USE WITH CAUTION**, monitor for adverse reactions related to itraconazole and/or diltiazem[c], dose reduction of itraconazole and/or diltiazem may be necessary.
Felodipine	Felodipine C_{max} ↑↑↑, AUC ↑↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of dihydropyridine-related adverse reactions, such as hypotension and peripheral edema.
Other dihydropyridines Verapamil	Dihydropyridine conc increase (extent unknown)[a,b] Verapamil conc increase (extent unknown)[a,b]	**USE WITH CAUTION**, monitor for dihydropyridine/verapamil adverse reactions[c], dose reduction of dihydropyridine/verapamil may be necessary.
Cardiovascular Drugs		

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Aliskiren Riociguat Sildenafil (pulmonary hypertension) Tadalafil (pulmonary hypertension)	Aliskiren C_{max} ↑↑↑, AUC ↑↑↑ Riociguat C_{max} (↑), AUC (↑↑)[a] Sildenafil/Tadalafil conc increase (extent unknown but effect may be greater than reported under Urologic Drugs)[a,b]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole[c]. Increased risk of adverse reactions related to the cardiovascular drug.
Bosentan Guanfacine	Bosentan C_{max} (↑↑), AUC (↑↑)[a] Guanfacine C_{max} (↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for bosentan/guanfacine adverse reactions[c], dose reduction of bosentan/guanfacine may be necessary.
Ivabradine	Ivabradine C_{max} (↑↑), AUC (↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ivabradine-related adverse reactions, such as atrial fibrillation, bradycardia, sinus arrest and heart block.
Ranolazine	Ranolazine C_{max} (↑↑), AUC (↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ranolazine-related adverse reactions, such as QT prolongation and renal failure.
Contraceptives*		
Dienogest Ulipristal	Dienogest C_{max} (↑), AUC (↑↑)[a] Ulipristal C_{max} (↑↑), AUC (↑↑↑)[a]	**USE WITH CAUTION**, monitor for contraceptive adverse reactions[c], refer to the dienogest/ulipristal PM for specific actions to be taken.
Diuretics		
Eplerenone	Eplerenone C_{max} (↑), AUC (↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of eplerenone-related adverse reactions, such as hyperkalemia and hypotension.
Gastrointestinal Drugs		
Aprepitant Loperamide	Aprepitant AUC (↑↑↑)[a] Loperamide C_{max} ↑↑, AUC ↑↑	**USE WITH CAUTION**, monitor for aprepitant/loperamide adverse reactions[c], Dose reduction of aprepitant/loperamide may be necessary.
Domperidone	Domperidone C_{max} ↑↑, AUC ↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of domperidone-related adverse reactions, such as serious ventricular arrhythmias and sudden cardiac death.
Naloxegol	Naloxegol C_{max} (↑↑↑), AUC (↑↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of naloxegol-related adverse reactions, such as opioid withdrawal symptoms.
Saccharomyces boulardii	*S. boulardii* colonization decrease (extent unknown)	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. S. boulardii efficacy may be reduced.

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Immunosuppressants		
Budesonide Ciclesonide Cyclosporine Dexamethasone Fluticasone Methylprednisolone Tacrolimus Temsirolimus	Budesonide (inhalation) C_{max} ↑, AUC ↑↑; Budesonide (other form.) conc increase (extent unknown)[a,b] Ciclesonide (inhalation) C_{max} (↑↑), AUC (↑↑)[a] Cyclosporine (iv) conc increase ↔ to ↑[b] Cyclosporine (other form.) conc increase (extent unknown)[a,b] Dexamethasone C_{max} ↔ (iv) ↑ (oral), AUC ↑↑ (iv, oral) Fluticasone (inhalation) conc increase ↑↑[b] Fluticasone (nasal) conc increase (↑)[a,b] Methylprednisolone (oral) C_{max} ↑ to ↑↑, AUC ↑↑ Methylprednisolone (iv) AUC ↑↑ Tacrolimus (iv) conc increase ↑[b] Tacrolimus (oral) C_{max} (↑↑), AUC (↑↑)[a] Temsirolimus (iv) C_{max} (↑↑), AUC (↑↑)[a]	**USE WITH CAUTION** monitor for immunosuppressant adverse reactions[c], Dose reduction of the immunosuppressant drug may be necessary.
Everolimus Sirolimus (rapamycin)	Everolimus C_{max} (↑↑), AUC (↑↑↑↑)[a] Sirolimus C_{max} (↑↑), AUC (↑↑↑↑)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole[c]. Increased risk of everolimus/ sirolimus-related adverse reactions.
Lipid Regulating Drugs		
Atorvastatin	Atorvastatin C_{max} ↔ to ↑↑, AUC ↑ to↑↑	**USE WITH CAUTION**, monitor for atorvastatin adverse reactions[c]. Dose reduction of atorvastatin may be necessary.
Lomitapide	Lomitapide C_{max} (↑↑↑↑), AUC (↑↑↑↑)[a]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of lomitapide-related adverse reactions, such as hepatotoxicity and severe gastrointestinal reactions.
Lovastatin Simvastatin	Lovastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑ Simvastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of lovastatin/simvastatin-related adverse reactions, such as myopathy, rhabdomyolysis and liver enzyme abnormalities.
Nonsteroidal Anti-Inflammatory Drugs		
Meloxicam	Meloxicam C_{max} ↓↓, AUC ↓	**USE WITH CAUTION**, monitor for reduced efficacy of meloxicam, dose adaption of meloxicam may be necessary.

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Respiratory Drugs		
Salmeterol	Salmeterol C_{max} (↑), AUC (↑↑↑↑)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of salmeterol-related adverse reactions[c].
SSRIs, Tricyclics and Related Antidepressants		
Reboxetine Venlafaxine	Reboxetine C_{max} (↔), AUC (↑)[a] Venlafaxine C_{max} (↑), AUC (↑)[a]	**USE WITH CAUTION**, monitor for reboxetine/venlafaxine adverse reactions[c], dose reduction of reboxetine/venlafaxine may be necessary.
Urologic Drugs		
Darifenacin Vardenafil	Darifenacin C_{max} (↑↑↑), AUC (↑↑↑ to ↑↑↑↑)[a] Vardenafil C_{max} (↑↑), AUC (↑↑↑↑)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of darifenacin/vardenafil-related adverse reactions[c].
Dutasteride Imidafenacin Oxybutynin Sildenafil (erectile dysfunction) Tadalafil (erectile dysfunction and benign prostatic hyperplasia) Tolterodine	Dutasteride conc increase (extent unknown)[a,b] Imidafenacin C_{max} ↑, AUC ↑ Oxybutynin conc increase ↑[b] Sildenafil C_{max} (↑↑), AUC (↑↑ to ↑↑↑↑)[a] Tadalafil C_{max} (↑), AUC (↑↑)[a] Tolterodine C_{max} (↑ to ↑↑), AUC (↑↑)[a] in poor metabolizers of CYP2D6	**USE WITH CAUTION**, monitor for urologic drug adverse reactions[c], dose reduction of the urologic drug may be necessary; refer to the dutasteride PM for specific actions to be taken. (For sildenafil and tadalafil, see also Cardiovascular Drugs, Miscellaneous Drugs and Other Substances in this table.)
Fesoterodine	Fesoterodine C_{max} (↑↑), AUC (↑↑)[a]	**CONTRAINDICATED** in patients with moderate to severe renal or hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of fesoterodine-related adverse reactions, such as severe anticholinergic effects. **USE WITH CAUTION** in other patients: monitor for fesoterodine adverse reactions[c], dose reduction of fesoterodine may be necessary.
Solifenacin	Solifenacin C_{max} (↑), AUC (↑↑)[a]	**CONTRAINDICATED** in patients with severe renal or moderate to severe hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of solifenacin-related adverse reactions, such as anticholinergic effects and QT prolongation. **USE WITH CAUTION** in other patients, monitor for solifenacin drug adverse reactions[c], dose reduction of solifenacin may be necessary.
Miscellaneous Drugs and Other Substances		

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Alitretinoin (oral) Cabergoline Cannabinoids Cinacalcet	Alitretinoin C_{max} (↑), AUC (↑)[a] Cabergoline C_{max} (↑↑), AUC (↑↑)[a] Cannabinoids conc increase, extent unknown but likely (↑↑)[a] Cinacalcet C_{max} (↑↑), AUC (↑↑)[a]	**USE WITH CAUTION**, monitor for alitretinoin/cabergoline/cannabinoids/ cinacalcet drug adverse reactions, dose reduction of alitretinoin/ cabergoline/cannabinoids/cinacalcet may be necessary[c].
Colchicine	Colchicine C_{max} (↑), AUC (↑↑)[a]	**CONTRAINDICATED** in patients with renal or hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of colchicine-related adverse reactions, such as decreased cardiac output, cardiac arrhythmias, respiratory distress and bone marrow depression. **NOT RECOMMENDED** in other patients, during and for 2 weeks after treatment with itraconazole. Increased risk of colchicine-related adverse reactions[c].
Eliglustat	CYP2D6 EMs: Eliglustat C_{max} (↑↑), AUC (↑↑)[a] Higher increases are expected in CYP2D6 IMs/PMs and upon coadministration with a CYP2D6 inhibitor.	**CONTRAINDICATED** in CYP2D6 EMs taking a strong or moderate CYP2D6 inhibitor / CYP2D6 IMs and PMs, during and for 2 weeks after treatment with itraconazole. Increased risk of eliglustat-related adverse reactions such as prolongation of the PR, QTc, and/or QRS cardiac interval, and cardiac arrhythmias. **USE WITH CAUTION** in CYP2D6 EMs, monitor for eliglustat adverse reactions[c], dose reduction of eliglustat may be necessary.
Ergot alkaloids	Ergot alkaloids conc increase (extent unknown)[a,b]	**CONTRAINDICATED** during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism. (see also Antimigraine Drugs in this table)
Galantamine	Galantamine C_{max} (↑), AUC (↑)[a]	**USE WITH CAUTION**, monitor for galantamine adverse reactions[c]. Dose reduction of galantamine may be necessary.
Ivacaftor	Ivacaftor C_{max} (↑↑), AUC (↑↑↑)[a]	**USE WITH CAUTION**, monitor for ivacaftor adverse reactions[c], dose reduction of ivacaftor may be necessary.
Lumacaftor/Ivacaftor	Ivacaftor C_{max} (↑↑), AUC (↑↑)[a] Lumacaftor C_{max} (↔), AUC (↔)[a] Itraconazole conc decrease, extent unknown but likely ↓↓↓	**NOT RECOMMENDED** from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of ivacaftor-related adverse reactions[c].
Vasopressin Receptor Antagonists		

Table 3: Examples of drugs that may interact with Itraconazole Oral Solution		
Medicinal products within class	**Expected/Potential effect on drug levels** (see footnotes for additional info)	**Clinical comment** (see codes above for additional info)
Conivaptan Tolvaptan	Conivaptan C_{max} (↑↑), AUC (↑↑↑↑)[a] Tolvaptan C_{max} (↑↑), AUC (↑↑↑)[a]	**NOT RECOMMENDED** during and for 2 weeks after treatment with itraconazole. Increased risk of conivaptan/ tolvaptan-related adverse reactions[c].
Mozavaptan	Mozavaptan C_{max} ↑, AUC ↑↑	**USE WITH CAUTION**, monitor for mozavaptan adverse reactions[c], dose reduction of mozavaptan may be necessary.

*CYP3A4 inhibitors (including itraconazole) may increase systemic contraceptive hormone concentrations EMs: extensive metabolizers; IMs: intermediate metabolizers, PMs: poor metabolizers; TdP: Torsade de Pointes

Note:

Average increase:

↑: <100% (i.e. <2-fold);
↑↑: 100-400% (i.e. ≥2-fold to <5-fold);
↑↑↑: 400-900% (i.e. ≥5-fold and <10-fold);
↑↑↑↑: ≥10-fold;

Average decrease:

↓: <40%;
↓↓: 40-80%;
↓↓↓: >80%;

No effect: ↔

For the effect (middle column) the name of the parent drug is stated, even when the effect is related to the active moiety or the active metabolite of a prodrug.

[a] For drugs with arrows between brackets, the assessment was based on the mechanism of interaction and clinical drug interaction information with ketoconazole or other strong CYP3A4 inhibitors and/or inhibitors of P-glycoprotein or BCRP, modelling techniques, case reports and/or *in vitro* data. For the other drugs listed, the assessment was based on clinical drug interaction information with itraconazole.

[b] Pharmacokinetic parameters were not available.

[c] Please consult the corresponding Product Monograph (PM) for information on drug-related adverse reactions

Drug-Food Interactions

For optimal absorption, ODAN ITRACONAZOLE oral solution should be taken without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

When ODAN ITRACONAZOLE oral solution may be indicated, the type of organism responsible for the infection should be isolated and identified; however, therapy may be initiated prior to obtaining these results, when clinically warranted.

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).

Special Populations

Pediatrics (< 18 years of age):

The safety and efficacy of itraconazole oral solution have not been established in pediatric patients. ODAN ITRACONAZOLE oral solution should not be used in pediatric patients unless the potential benefit outweighs the potential risks (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Geriatrics (> 65 years of age):

Clinical data on the use of itraconazole oral solution in elderly patients are limited. It is advised to use ODAN 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.

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 **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**; **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

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. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered (see **WARNINGS AND PRECAUTIONS**, **Renal; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**, **Renal Insufficiency**).

Recommended Dose and Dosage Adjustment

Oral Candidiasis: The recommended dosage of itraconazole oral solution for oral candidiasis is 200 mg (20 mL of oral solution) daily in a single dose or divided doses; treatment should continue for 1-2 weeks to decrease the likelihood of relapse.

Esophageal Candidiasis: The recommended dosage for esophageal candidiasis is 100 mg (10 mL of oral solution) daily for a minimum treatment of three weeks. Treatment should continue for two weeks following resolution of symptoms. Doses of up to 200 mg (20 mL of oral solution) per day may be used based on medical assessment of the patient's response to therapy.

Administration

The solution should be swished in the oral cavity and swallowed. There should be no rinsing after swallowing.

OVERDOSAGE

There is no experience of overdosage with itraconazole oral solution; however, based on animal toxicity data, symptoms of a gastrointestinal or central nervous system nature may be expected to occur.

Although no data are available for itraconazole, standard supportive treatment should be applied as necessary.

It has been reported that itraconazole cannot be removed by hemodialysis. No specific antidote is available.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Itraconazole, a triazole derivative, has a broad-spectrum activity; with respect to *Candida* spp., its activity includes *C. albicans*, *C. glabrata* and *C. krusei*.

In vitro studies have demonstrated that itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is a vital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.

Pharmacodynamics

See **DETAILED PHARMACOLOGY**.

Pharmacokinetics

Absorption: The oral bioavailability of itraconazole is maximal when itraconazole oral solution is taken without food. During chronic administration, steady-state is reached after 1-2 weeks. Peak plasma levels are observed 2 hours (fasting) to 5 hours (with food) following administration of the oral solution. After repeated once-a-day administration of itraconazole 200 mg in fasting condition, steady-state plasma concentrations of itraconazole fluctuate between 1 and 2 μg/mL (trough to peak). When the oral solution is taken with food, steady-state plasma concentrations of itraconazole are about 25% lower.
Itraconazole exposure is greater with the oral solution than with the capsule formulation when the same dose of drug is given (see **DETAILED PHARMACOLOGY, Human Pharmacokinetics,** Absorption).

Distribution: The plasma protein binding of itraconazole is 99.8%. Itraconazole is extensively distributed into tissues that are prone to fungal invasion. Concentrations in human lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than the corresponding plasma concentrations 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.

Metabolism: Itraconazole is extensively metabolized 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 a

comparable antifungal activity to itraconazole. Trough plasma levels of hydroxy-itraconazole are about two times higher than those of itraconazole.

Excretion: Itraconazole is excreted mainly as inactive metabolites in urine (35%) and in feces (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. After repeated oral administration, elimination of itraconazole from plasma is biphasic with a terminal half-life of 1.5 days. Based on an oral radiolabelled dose, fecal excretion of the unchanged drug ranges from 3%-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 and Conditions

Pediatrics: Limited pharmacokinetic data are available on the use of itraconazole in the pediatric population. A clinical pharmacokinetic study in children and adolescents aged between 6 months and 12 years was conducted with itraconazole oral solution. Patients were stratified by age, and received itraconazole oral solution 5 mg/kg once daily for 14 days. Pharmacokinetic parameters at steady state (Day 14) were not significantly different among the age strata (see **DETAILED PHARMACOLOGY, Human Pharmacokinetics**, Pediatric Patients).
Geriatrics: No data are available in geriatric patients.

Hepatic Insufficiency: Itraconazole is predominantly metabolized in the liver. Pharmacokinetic data for patients with hepatic insufficiency is limited to subjects who received a single 100 mg dose of itraconazole capsules. 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 mean C_{max} (47%; mean cirrhotic C_{max} 87 ± 18 ng/mL, mean healthy C_{max} 164 ± 34 ng/mL) and a two-fold increase in the elimination half-life (37 ± 7 hrs and 16 ± 5 hrs, respectively) 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 (mean cirrhotic AUC 1449 ± 207 ng.h/mL, mean healthy AUC 1856 ± 388 ng.h/mL). Data are not available in cirrhotic patients during long-term use of itraconazole. Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in cirrhotic patients should be considered when deciding to initiate therapy with other medicines metabolized by CYP3A4 (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Renal Insufficiency: Limited data are available on the use of itraconazole in patients with renal insufficiency. Pharmacokinetic data in renally impaired patients is limited to subjects who received a single 200 mg dose of itraconazole capsules. 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; continuous ambulatory peritoneal dialysis: n=5). Mean ± SD pharmacokinetic parameters are summarized in Table 4.

Table 4: **Mean pharmacokinetic parameters in renally impaired patients receiving a single 200 mg oral dose of itraconazole**

Patient Group (n)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-8h} (ng.h/mL)
Uremic (7)	4.0 ± 1.2	213 ± 178	1026 ± 819
Hemodialysis			
Off dialysis (7)	4.7 ± 1.4	140 ± 119	634 ± 507
On dialysis (7)	4.1 ± 0.9	113 ± 83	507 ± 371
CAPD (5)	4.4 ± 2.2	77 ± 29	325 ± 107

Plasma concentration vs. time profiles showed wide inter-subject variation in all three groups. In uremic subjects (mean CrCl 13 mL/min/1.73m^2), mean plasma concentrations and overall exposure, based on AUC_∞, were slightly reduced compared with healthy subject in a previous study (AUC_∞ values of 3454 ± 3132 vs. 4161 ± 1949 ng h/mL in uremic patients and healthy subjects, respectively). C_{max} and AUC_{0-8h} values were reduced 30-40% in hemodialysis patients on non-dialysis days, compared to uremic patients (see Table 4), and further reduced 10-20% on dialysis days. In CAPD patients, C_{max} and AUC_{0-8h} values were reduced to one-third the values seen in non-dialyzed uremic patients.

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 **WARNINGS AND PRECAUTIONS, Renal** and **DOSAGE AND ADMINISTRATION,** Patients with Renal Impairment).

Cystic Fibrosis: In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady-state dosing of oral solution using 2.5 mg/kg b.i.d. Steady-state concentrations of > 250 ng/mL were achieved in approximately 50% of subjects greater than 16 years of age, but in none of the patients less than 16 years of age. If a patient does not respond to ODAN ITRACONAZOLE oral solution, consideration should be given to switching to alternative therapy.

STORAGE AND STABILITY

ODAN ITRACONAZOLE oral solution should be stored at 15°C – 30 °C. Discard remaining unused product three months after opening bottle. Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Each millilitre of ODAN ITRACONAZOLE oral solution contains 10 mg of itraconazole as well as: hydroxypropyl-ß-cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour, sodium saccharin, sodium hydroxide and purified water.

Dosage Forms and Packaging

ODAN ITRACONAZOLE oral solution is available as a 10 mg itraconazole per mL solution, with 150 mL in each amber glass bottle.

A graduated dosing cup is supplied with the ODAN ITRACONAZOLE oral solution. The dosing cup is provided in the package to accurately measure the amount of solution needed. ODAN ITRACONAZOLE oral solution should be poured into the end of the cup with the graduations which indicate dosing amounts (5 mL to 30 mL, in increments of 5 mL).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

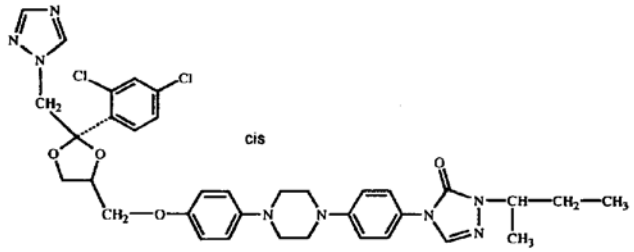
Drug Substance

Proper name: Itraconazole

Chemical name: (±)-cis-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one

Molecular formula and molecular mass: $C_{35}H_{38}Cl_2N_8O_4$, 705.64 g/mol

Structural formula:



Physicochemical properties: Itraconazole is an almost white to slightly yellow powder, with a pKa of 3.7 and a melting range of 165-169°C. It is highly hydrophobic and lipophilic, with a log partition coefficient of 5.66 in the n-octanol/aqueous buffer solution of pH=8.1.

Itraconazole is very poorly soluble in water (<1 µg/mL) and in diluted acidic solutions (<5 µg/mL).

Concentrations exceeding 1% can only be obtained in some organic solvents such as acidified polyethylene glycols (PEG) or in aqueous cyclodextrin solutions.

CLINICAL TRIALS

Oropharyngeal Candidiasis

Table 5: Summary of patient demographics for clinical trials in oropharyngeal candidiasis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (total/efficacy)[a]	Mean age (Range)[b]	Gender (M/F)[b]
ITR-USA-7	third-party blinded, active-controlled	itraconazole oral solution 200 mg o.d. for 7 days	n=64/60	38 (25-67)	56/8
		itraconazole oral solution 200 mg o.d. for 14 days	n=64/59	36.5 (21-67)	62/2
		fluconazole tablet 100 mg o.d. for 14 days	n=62/60	37.5 (24-61)	58/4
ITR-INT-27	multicentre, randomized, double-blind, double-dummy, active-controlled	itraconazole oral solution 100 mg b.i.d. for 7 days	n=79/68	37 (22-64)	72/7
		itraconazole oral solution 100 mg o.d. for 14 days	n=79/68	35 (24-58)	70/9
		fluconazole tablet 100 mg o.d. for 14 days	n=86/78	36 (21-66)	79/7
ITR-USA-94	uncontrolled, open-label	itraconazole oral solution, 100 mg b.i.d. for 14-28 days based on response	n=74/68	37 (20-60)	68/6

[a] Total: intent-to-treat population; Efficacy: patients included in efficacy analysis
[b] values based on total number of study subjects

Two randomized, controlled studies for the treatment of oropharyngeal candidiasis have been conducted. In one trial (n=179, all patients HIV-seropositive), clinical response (a global clinical evaluation of cured or improved) was not significantly different for patients treated with fluconazole tablets, 100 mg/day for 14 days (52/60; 87%), or itraconazole oral solution, 200 mg/day given for 7 days (50/60; 83%) or 14 days (57/59; 97%). Response to 14 days therapy with itraconazole oral solution was associated with a lower relapse rate than response to 7 days therapy with itraconazole oral solution. In the other trial (n=214, all HIV-seropositive patients), clinical response was not significantly different for patients treated with itraconazole oral solution 200 mg/day for 14 days, itraconazole oral solution 100 mg/day for 14 days or fluconazole 100 mg/day for 14 days. Response was 56/68 (84%), 62/68 (91%) and 71/78 (91%) for patients treated with a daily dose of itraconazole oral solution 200 mg, itraconazole oral solution 100 mg and fluconazole 100 mg, respectively.

In an uncontrolled, open-label study of selected patients clinically unresponsive to fluconazole tablets (n=74, all patients HIV-seropositive), patients were treated with itraconazole oral solution 100 mg b.i.d. (clinically unresponsive to fluconazole in this study was defined as having received a dose of fluconazole tablets at least 200 mg/day for a minimum of 14 days). Treatment duration was 14-28 days based on response.

The mean CD4 count of these patients was 23/mm^3. Approximately 55% of patients had complete resolution of oral lesions. Of patients who responded and then entered a follow-up phase (n=22), all relapsed within a month when treatment was discontinued, with a median time to relapse of 14 days. Although baseline endoscopies had not been performed, several patients in this study developed symptoms of esophageal candidiasis while receiving treatment with itraconazole oral solution. Itraconazole oral solution has not been directly compared to other agents in a controlled trial of similar patients.

Esophageal Candidiasis

Table 6: Summary of patient demographics for clinical trials in esophageal candidiasis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (total/efficacy)[b]	Mean age (Range)[c]	Gender (M/F)[c]
ITR-USA-12	double-blind, randomized, active-controlled	itraconazole oral solution 100-200 mg o.d. for 3-8 wks[a]	n=63/53	38 (24-57)	53/10
		fluconazole tablet 100-200 mg o.d.	n=63/57	37 (23-62)	55/8

[a] Treatment continued for two weeks beyond resolution of symptoms, but not less than 3 weeks nor more than 8 weeks
[b] Total: intent-to-treat population; Efficacy: patients included in efficacy analysis
[c] values based on total number of study subjects

A double-blind, randomized study (n=110, 102 of whom were HIV-seropositive) compared itraconazole oral solution (100 mg/day) to fluconazole tablets (100 mg/day). The dose of each was increased to 200 mg/day for patients not responding initially. Treatment continued for 2 weeks following a resolution of symptoms for a total duration of 3-8 weeks. Clinical response (a global clinical assessment of cured or improved) was not significantly different between the two study arms and was >90% for both arms. Six of 53 (11%) itraconazole patients and 12 of 57 (21%) fluconazole patients were escalated to the 200 mg dose in this trial. Of the subgroup of patients who responded and entered a follow-up phase (n=88), approximately 23% relapsed across both arms within 4 weeks.

Oral and/or Esophageal Candidiasis

Table 7: Summary of patient demographics for clinical trials in oral and/or esophageal candidiasis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (total/efficacy)[a]	Mean age (Range)[b]	Gender (M/F)[b]
ITR-FRA-5	uncontrolled, open-label	Week 1-2: itraconazole oral solution 100 mg b.i.d. Week 3-4 in case of failure: itraconazole oral solution 200 mg b.i.d.	n=60/40	38 (25-69)	50/10

[a] Total: intent-to-treat population; Efficacy: patients included in efficacy analysis
[b] values based on total number of study subjects

An uncontrolled, open-label study (n=40, all patients HIV-seropositive) treated patients clinically unresponsive or refractory to fluconazole tablets (defined as a dose of fluconazole tablets 100-200 mg/day for a minimum of 14 days) with itraconazole oral solution, 100 mg b.i.d. for 14 days. If not cured, itraconazole oral solution treatment was continued at 400 mg b.i.d. for another 14 days. Sixty percent of the evaluable patients had sufficient improvement at week 2; 70% of the patients were clinically cured at the end of treatment period.

DETAILED PHARMACOLOGY

Human Pharmacodynamics

In vitro

A 50% inhibition of the cholesterol biosynthesis is obtained in vitro in human lymphocytes with itraconazole at a concentration of 4×10^{-7}M, which is more than 100 times the concentration of itraconazole needed to produce a 50% inhibition of the ergosterol synthesis in *Candida albicans*.

Up to a concentration of 10^{-5}M, itraconazole did not inhibit the cytochrome P-450 dependent aromatization of androstenedione to estrogens by human placental microsomes.

In vivo

In male volunteers, basal serum levels of cholesterol remained similar to the control values obtained before itraconazole treatment of 100 mg o.d. for 1 month.

Long-term administration of itraconazole (up to 400 mg/day for up to a maximum of 2 years) indicated a slight decrease in plasma cholesterol in 67 patients who had a baseline cholesterol plasma level higher than 200 mg/dL.

Only 9.5% of patients showed a shift to a somewhat higher plasma cholesterol level. Similar results were observed in 29 patients with baseline cholesterol levels of at least 250 mg/dL and itraconazole therapy (50-400 mg/day) for a minimum of 3 months. Twenty-three patients showed a reduction and six patients had an increased cholesterol level. In this study, the overall decrease in cholesterol did not coincide with alterations in the triglyceride levels.

There was no significant effect of itraconazole 100 or 200 mg taken daily for 35 days on the serum levels of 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol in 12 volunteers.

In volunteers receiving single or multiple doses of itraconazole for up to 30 days, no effect on serum levels of the following hormones were observed: basal plasma cortisol, testosterone, aldosterone, cortisol response to cosyntropin (ACTH) and plasma prolactin and response of plasma prolactin, follicle stimulating hormone (FSH) and luteinizing hormone (LH) to an intravenous luteinizing hormone releasing hormone (LHRH) challenge.

Plasma progesterone and estradiol levels measured once weekly (before, during and for 2 weeks after a 5-week administration period of itraconazole 200 mg/day) and saliva progesterone concentrations measured daily during the 5-week administration, reflected a totally normal hormonal profile throughout the menstrual cycle.

In healthy female volunteers with normal, regular menstrual cycles, a single 300 mg dose of itraconazole taken during the late follicular phase did not modify the circadian variation in plasma 17β-estradiol levels. The same dose taken during the luteal phase had no effects on 17β-estradiol and progesterone levels.

Male patients with superficial mycoses who received 50 or 100 mg itraconazole for up to 2 months showed no change in levels of testosterone, sex hormone binding globulin (SHBG), luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol.

In 15 patients with systemic mycoses receiving 200 to 400 mg/day itraconazole, adrenal function was studied before and after 12.4 ± 5 (7-24) months of treatment. No change in the response of plasma cortisol to ACTH stimulation was observed. Average testosterone values measured in these patients before and after itraconazole were not statistically significantly different. However, one of eight patients treated with itraconazole 600 mg/day for severe or refractory systemic fungal infection demonstrated a blunted cortisol response after one month of treatment. Reduction of the dose to 400 mg/day was associated with resolution of the symptoms associated with adrenal insufficiency and an improved cortisol response.

The administration of 200 mg itraconazole daily for 5 weeks had no significant influence on the heart rate, blood pressure, ECG intervals and systolic time intervals in volunteers. This finding was confirmed in cancer patients who received 50 mg itraconazole daily for 48 weeks.

In six healthy volunteers, itraconazole 200 mg daily did not seem to have a negative influence on immune functions. After 5 weeks of itraconazole treatment, only values for OKT4 positive lymphocyte showed a significant shift from 42 ± 3.3% to 53 ± 3.3%. This increase as well as shifts in the other immunological parameters remained within the normal ranges.

Animal Pharmacodynamics

In general observation tests, the dose of 40 mg/kg, given orally to mice and injected intraperitoneally in rats, was devoid of central actions. In addition, many peripheral (anticholinergic, antidiarrheal, α_1-adrenergic blocking, muscle relaxant, aspirin-like activation) and non-specific actions (hypothermic, toxic) can be excluded from its activity profile.

Itraconazole, at the oral dose of 40 mg/kg in rats was found to be devoid of effects on: conditioned food consumption; fecal excretion; urine excretion; castor oil diarrhea; tail withdrawal reaction time; Mycobacterium butyricum arthritis (36 mg/kg in the food); and gastric mucosal integrity (40 mg/mL or 100 mg/kg in 0.15 M HCl). Whenever any effects of itraconazole dissolved in PEG 200 were observed, they were identical to those seen with the vehicle alone.

Human Pharmacokinetics

Absorption

The absolute bioavailability of itraconazole administered as a non-marketed solution formulation under fed conditions was 55% in six healthy male volunteers. However, the bioavailability of itraconazole oral solution is increased under fasted conditions reaching higher maximum plasma concentrations (C_{max}) in a shorter period of time. In 27 healthy male volunteers, the steady-state area under the plasma concentration versus time curve (AUC_{0-24}) of itraconazole (itraconazole oral solution, 200 mg daily for 15 days) under fasted conditions was 131 ± 30% of that obtained under fed conditions. Therefore, unlike itraconazole

capsules, it is recommended that itraconazole oral solution be administered without food. Presented in Table 8 below are the steady-state (Day 15) pharmacokinetic parameters for itraconazole and hydroxy-itraconazole (itraconazole oral solution) under fasted and fed conditions.

Table 8: Steady-state pharmacokinetic parameters for itraconazole and hydroxy-itraconazole under fasted and fed conditions.

	Itraconazole		Hydroxy-itraconazole	
	Fasted	Fed	Fasted	Fed
C_{max} (ng/mL)	1963 ± 601*	1435 ± 477	2055 ± 487	1781 ± 397
T_{max} (hours)	2.5 ± 0.8	4.4 ± 0.7	5.3 ± 4.3	4.3 ± 1.2
AUC_{0-24} (ng≅h/mL)	29271 ± 10285	22815 ± 7098	45184 ± 10981	38823 ± 8907
$t_{1/2}$ (hours)	39.7 ± 13	37.4 ± 13	27.3 ± 13	26.1 ± 10

*mean ± standard deviation

The bioavailability of itraconazole oral solution relative to itraconazole capsules was studied in 30 healthy male volunteers who received 200 mg of itraconazole as the oral solution and capsules under fed conditions. The $AUC_{0-\infty}$ from itraconazole oral solution was 149 ± 68% of that obtained from itraconazole capsules; a similar increase was observed for hydroxy-itraconazole. In addition, a cross-study comparison of itraconazole and hydroxy-itraconazole pharmacokinetics following the administration of single 200 mg doses of itraconazole oral solution (under fasted conditions) or itraconazole capsules (under fed conditions) indicates that when these two formulations are administered under conditions which optimize their systemic absorption, the bioavailability of the solution relative to capsules is expected to be increased further. Therefore, it is recommended that itraconazole oral solution and itraconazole capsules not be used interchangeably. Table 9 contains pharmacokinetic parameters for itraconazole and hydroxy-itraconazole following single 200 mg doses of itraconazole oral solution (n=27) or itraconazole capsules (n=30) administered to healthy male volunteers under fasted and fed conditions, respectively.

Table 9: Pharmacokinetic parameters for itraconazole and hydroxy-itraconazole in healthy male volunteers under fed and fasted conditions

	Itraconazole		Hydroxy-itraconazole	
	Oral Solution fasted	Capsules fed	Oral Solution fasted	Capsules fed
C_{max} (ng/mL)	544 ± 213*	302 ± 119	622 ± 116	504 ± 132
T_{max} (hours)	2.2 ± 0.8	5 ± 0.8	3.5 ± 1.2	5 ± 1
AUC_{0-24} (ng≅h/mL)	4505 ± 1670	2682 ± 1084	9552 ± 1835	7293 ± 2144

*mean ± standard deviation

HIV-Positive Patients:
The bioavailability of itraconazole oral solution was investigated in two groups of HIV-positive patients characterized by the severity of their HIV infection. The first group consisted of 12 patients with CD4 count > 200/mm^3 and no AIDS; the second group included 11 patients with CD4 count < 100/mm^3 and AIDS. At 100 mg b.i.d. for 15 days, both groups displayed satisfactory plasma concentrations and the bioavailability was equivalent in both groups. Table 10 summarizes the study results.

Table 10: Plasma concentrations (ng/mL) of itraconazole and hydroxy-itraconazole after repeated administration of itraconazole oral solution in HIV-positive patients

Day	HIV-positive patients with CD4 count > 200/mm^3		AIDS patients with CD4 count < 100/mm3	
	Itraconazole	Hydroxy-itraconazole	Itraconazole	Hydroxy-itraconazole
2	112 ± 45*	310 ± 121	95 ± 84	258 ± 156
4	305 ± 93	771 ± 211	271 ± 189	688 ± 346
7	443 ± 189	1105 ± 343	424 ± 281	1034 ± 524
13	585 ± 250	1302 ± 511	587 ± 377	1339 ± 731
15	645 ± 303	1481 ± 563	583 ± 414	1355 ± 800

*mean ± standard deviation

Pediatric Patients:
The pharmacokinetics of itraconazole oral solution were studied in 26 pediatric patients requiring systemic antifungal therapy. Patients were stratified by age: 6 months to 2 years (n=8), 2 to 5 years (n=7) and 5 to 12 years (n=11), and received itraconazole oral solution 5 mg/kg once daily for 14 days. Pharmacokinetic parameters at steady state (Day 14) were not significantly different among the age strata and are summarized in Table 11 below for all 26 patients.

Table 11: Pharmacokinetics of itraconazole oral solution in pediatric patients

	Itraconazole	Hydroxy-itraconazole
C_{max} (ng/mL)	582.5 ± 382.4*	692.4 ± 355.0
C_{min} (ng/mL)	187.5 ± 161.4	403.8 ± 336.1
AUC_{0-24} (ng·h/mL)	7706.7 ± 5245.2	13356.4 ± 8942.4
$t_{1/2}$ (hours)	35.8 ± 35.6	17.7 ± 13.0

*mean ± standard deviation

Distribution
The plasma protein binding of itraconazole is 99.8% and that of hydroxy-itraconazole is 99.5%.

Concentrations of itraconazole in whole blood are 60% of those in plasma. Uptake in keratinous tissues, especially the skin, is up to five times higher than in plasma, and elimination of itraconazole is related to epidermal regeneration. Therefore, therapeutic levels in the skin persist for 2 to 4 weeks after discontinuation of a 4-week treatment. Itraconazole is also present in sebum and to a lesser extent in sweat. Itraconazole is extensively distributed into tissues which

are prone to fungal invasion. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than the corresponding plasma concentration.

Metabolism and Excretion

Itraconazole is extensively metabolized by the liver into a large number of metabolites. One of the metabolites is hydroxy-itraconazole, which has antifungal activity comparable to itraconazole in vitro. Antifungal drug levels measured by bioassay were about three times those of itraconazole assayed by high-performance liquid chromatography. Fecal excretion of the parent drug varies between 3%-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. One week after oral administration of radiolabelled itraconazole, urinary excretion of total radioactivity amounted to 35% of the dose and fecal excretion represented 54% of the dose. The main metabolic pathways were oxidative scission of the dioxolane ring, aliphatic oxidation at the 1-methylpropyl substituent, N-dealkylation of this 1-methylpropyl substituent, oxidative degradation of the piperazine ring and triazolone scission.

Animal Pharmacokinetics

The absorption, tissue distribution, metabolism and excretion of itraconazole were studied in rats, mice, rabbits and dogs.

Following single oral administration, itraconazole was well absorbed in all species studied. The absolute bioavailability of oral itraconazole in the fasting dog was 48% for the drug given in an aqueous β-cyclodextrin solution and 10%-30% for PEG-capsules. After a single oral dose of ^{3}H-itraconazole, the unchanged drug represented on average 20%-26% of the plasma radioactivity in rats, 15% in dogs and 10% in man. The terminal plasma half-life of itraconazole was 7 hours in male rats and in rabbits, 16 hours in female rats and about 50 hours in dogs.

Hydroxy-itraconazole was the main plasma metabolite in all species studied, and showed an antifungal activity similar to that of itraconazole. The mean AUC ratio of hydroxy-itraconazole to unchanged itraconazole was 1.1 in dogs. The terminal half-life of hydroxy-itraconazole was about 35 hours in dogs.

On repeated administration, steady state was reached within 6 days in rats and rabbits and within 14 days in dogs. Average steady-state levels of itraconazole increased proportionally with the dose in rabbits (5 to 80 mg/kg) and dogs (2.5 to 20 mg/kg) and values were consistent with those predicted from single-dose kinetics. In dogs, apparent dose-dependent kinetics were observed for doses higher than 20 mg/kg, due to the limited solubility of the drug in the gastrointestinal fluid. In both dog and man, AUC ratios of hydroxy-itraconazole to itraconazole after repeated administration were similar to those after a single oral dose. In male rats and in male and female mice, there appeared to be a dose-dependent formation of hydroxy-itraconazole, with plasma concentration ratios of hydroxy-itraconazole to itraconazole decreasing from about 3 at 10 mg/kg to 0.5-0.8 at 160 mg/kg.

The plasma protein binding of itraconazole was very high in rats (99.73%) and in dogs (99.79%). The plasma protein binding of hydroxy-itraconazole was very high too, but somewhat lower than that of the parent drug. Nevertheless, the tissue distribution of itraconazole as well as of hydroxy-itraconazole was extensive, as demonstrated by in vivo tissue distribution studies in rats and dogs, and as reflected by the high volume of distribution of itraconazole in dogs (17 L/kg). Highest radioactivity levels were seen in the adrenal gland, in liver, in lacrimatory gland and in fat. Remarkably high concentrations were found in the vaginal fluid and tissue. In most other

tissues, including the skin, radioactivity levels were about two to five times higher than the corresponding plasma levels. Lowest levels at any time point occurred in the blood and brain.

Brain to plasma ratios were about 1. After peak time, tissue levels in female rats were 2 to 4 times higher than in males. Most tissue to plasma concentration ratios of hydroxy-itraconazole were comparable to those of itraconazole in male and female rats, whereas in dog tissues they were about half those of the parent drug. The elimination rate of itraconazole as well as of hydroxy-itraconazole from rat tissues was similar to that from plasma. Placental transfer of itraconazole in the rat was very limited, since only 0.9% of the maternal dose was recovered in the combined fetuses. No undue accumulation occurred either in rats or in dogs after subchronic or chronic administration of itraconazole at very high doses.

The excretion of the radioactivity in rats was very rapid. The predominant excretion in the feces (90%) was related to an extensive biliary excretion (63% in male rats, part of which underwent enterohepatic circulation) and to the excretion of the parent drug (22%-29%). In dogs the excretion was slower and amounted to 17% in the urine and 65% in the feces within one week.

Itraconazole was metabolized into more than 30 metabolites in both rats and dogs and in man. The metabolic pathways were very similar in the three species. There were some quantitative differences for the mass balance of the metabolites in the three species, but all metabolites detected in man were found to some extent also in rats and dogs, both species used in toxicity experiments. Besides hydroxy-itraconazole, which resulted from the (ω-1)-oxidation at the 1-methylpropyl substituent, there were no other antifungally active metabolites.

MICROBIOLOGY

Itraconazole is an orally active triazole antifungal drug which demonstrates antifungal activity on a wide variety of fungi and yeast in vitro. This spectrum includes dermatophytes (e.g., *Microsporum, Trichophyton* and *Epidermophyton* species), yeasts (e.g., *Candida spp*. including *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*, *Cryptococcus neoformans, Malassezia* spp.); dimorphic fungi (e.g., *Histoplasma* including *H. capsulatum; Paracoccidioides brasiliensis, Blastomyces dermatitidis* and *Sporothrix schenckii*), various organisms which cause chromomycosis, and other fungi including *Aspergillus fumigatus*.

MIC_{90}'s for the majority of medically important fungi are between 0.1 and 1.0 µg/mL, while fungicidal activity is obtained at higher concentrations (10 µg/mL). The in vitro activity of hydroxy-itraconazole (the only active metabolite) is comparable to the in vitro activity of itraconazole.

The spectrum of in vitro antifungal activity of itraconazole in brain heart infusion is represented in Table 12.

Table 12: Spectrum of in vitro antifungal activity of itraconazole in brain heart infusion

Fungi	Number tested		Cumulative percentage of strains sensitive at stated concentration (in µg/mL)						
	Species	Strains	0.001	0.01	0.1	1	10	100	>100
Dermatophytes	19	456	3	18.6	94.1	99.3	100	100	
Candida albicans	1	1401	0.2	8.6	71.0	98.1	99.8		
Other *Candida spp*.	17	267	1.9	22.5	87.6	98.1	99.6	100	
Torulopsis spp.	5	245	1.2	10.6	87.3	97.6	99.6	100	
Cryptococcus neoformans	1	33	3	60.6	100	-			
Pityrosporum ovale[1]	1	35	0	0	91.4	100			
Various yeasts	6	55	20	47.3	72.7	92.7	96.4	100	
Aspergillus fumigatus	1	83	0	7.2	68.7	98.8	100		
Various *Aspergillus* & *Penicillium spp*.	19	57	1.8	3.5	63.2	80.1	93.0	100	
Sporothrix schenckii	1	23	0	0	78.3	100			
Dimorphic fungi MP	4	10	30	80	100				
Dimorphic fungi YP	4	10	50	100					
Phaeohyphomycetes	11	27	14.8	29.6	96.3	100			
Enfungi (mycetoma)	10	13	7.7	30.8	76.9	84.6	84.6	92.3	100
Phycomycetes	13	23	4.3	4.3	26.1	73.9	82.6	100	
Various other fungi	27	65	1.5	4.6	33.8	44.6	53.8	75.4	100
Actinomycetales	9	10	0	0	10	10	20	70	100

[1] Test medium: Dixon broth

From: Van Cutsem J, Van Gerven F, Janssen PAJ. The in vitro and in vivo antifungal activity of itraconazole. In: Fromtling RA, ed. Recent trends in the discovery, development and evaluation of antifungal agents. Telesymposia proceedings. Barcelona: J.R. Prous Science Publishers, 1987;182.

In vitro results vary considerably depending on culture medium, inoculum size, conditions of incubation, etc. Because of this variability of in vitro results, most fungi show a higher apparent sensitivity to itraconazole in vivo. The in vivo activity of oral itraconazole observed in experimental animal models of systemic mycoses is shown in Table 13. The principal fungus types that are not inhibited by itraconazole in vitro are *Zygomycetes* (e.g. *Rhizopus spp*., *Rhizomucor spp*., *Mucor spp.* and *Absidia spp*.), *Fusarium spp*., *Scedosporium spp*. and *Scopulariopsis spp*.

Candida krusei, *Candida glabrata* and *Candida tropicalis* are generally the least susceptible *Candida* species, with some isolates showing unequivocal resistance to itraconazole in vitro.

Table 13: In vivo activity of oral itraconazole

Infection	Animal	Delay/ duration[a] (days)	% of animals responding at dosage indicated (mg/kg/day)								Response
			1.25	2.5	5	10	20	40	80	160	
Candidiasis	Guinea pig	0/14	27		96						Negative kidney culture
	Rat	0/3		100							Survived 21 days
	Rabbit	+1/7							86[b]		Negative kidney culture
Aspergillosis	Guinea pig	0/14			83	75					Survived 28 days
	Guinea pig	%0/14			50	83					Survived 28 days
	IC[d] guinea pig	0/28			100						Survived 28 days
	IC[d] guinea pig	%1/28			80						Survived 28 days
	Mouse	0/5							47		Negative kidney culture
	Rabbit[c]	%3/14			100						Cured
Cryptococcosis	Guinea pig	+3/35				88	100				Negative culture (CSF excluded)
	Mouse	0/14								53	Negative CSF culture
	Rabbit	+4/14							73[b]		Negative CSF culture
Sporotrichosis	Guinea pig	0/28					80	100			Cured
Histoplasmosis	Guinea pig	0/14				63		100			Cured
Coccidioidomy-cosis	Rat	- 3/14					100[e]				Negative lung culture
	Rat	%7/14					80[e]				Negative lung culture
Paracoccidioid-omycosis	Mouse	0/28				100					Survived 28 days

[a] Delay in start of treatment relative to time of infection/duration of treatment.
[b] 200 mg given to each animal, roughly equivalent to 80 mg/kg/day.
[c] Itraconazole administered intravenously.
[d] IC = immunocompromised by cyclophosphamide, corticosteroids or mechlorethamine.
[e] Actual dosage 16 mg/kg/day.
From: Grant SM, Clissold SP. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. Drugs 37;1989:319.

Resistance and Cross-Resistance

A three-day treatment with itraconazole did not decrease the sensitivity of *C. albicans, T. glabrata,* or *C. krusei* to the drug. Similarly, the sensitivity of *M. furfur* was not decreased with a 3-week treatment of itraconazole. Furthermore, after 6 months of itraconazole treatment (200 mg twice weekly), no significant changes in IC_{50} were observed in 250 isolates of *C. albicans* tested. However, the development of resistance and the effects of long-term administration with a wider range of fungal species have not been systematically evaluated.

Cross-resistance of strains to azole antifungal agents has been known to occur.

TOXICOLOGY

Single-Dose Toxicity

Itraconazole/(HP-β-CD) was administered orally and intravenously to mice, rats and dogs from both genders. The results are summarized in Table 14.

Table 14: Single-dose toxicity studies with itraconazole/(HP-β-CD)

Species	Route	Sex	LD_{50}-values (mg itraconazole/(HP-β-CD)/kg bwt)
mouse	oral	M & F	> 100/(2500)
mouse	intravenous	M & F	> 44.1/(1764)
rat	oral	M & F	> 100/(2500)
rat	intravenous	M & F	> 17.6/(704)
dog	oral	M & F	> 100/(2500)
dog	intravenous	M & F	> 17.6/(704)

Upon oral administration, all animals survived the maximum dose of 100/(2500) mg/kg body weight (bwt). Clinical responses mainly consisting of soft feces or diarrhea were seen in all three species. As they were also present in the mice and rats dosed with HP-β-CD alone, these phenomena were considered to be due to the osmotic effects of HP-β-CD.

A single intravenous dose of 44.1/(1764) mg/kg bwt in mice and 17.6/(704) mg/kg bwt in rats and dogs did not result in mortality. Clinical effects observed were transient hyperpnea in rats and mice, and dyspnea and loss of righting reflex in dogs. These effects were only seen during the first hours after injection.

Long-Term Toxicity

For the evaluation of repeated oral use of itraconazole/(HP-β-CD), mice, rats and dogs were daily dosed for 3 months. In addition, chronic oral toxicity studies were performed in rats (6 months) and dogs (12 months). The duration of these studies was done in conformity with the requirements of the major regulatory authorities worldwide.

Table 15: Doses of itraconazole/(HP-β-CD) in studies in mice, rats and dogs

Study	itraconazole/(HP-β-CD) doses in mg/kg bwt
3 month pilot toxicity in mice	0/(0), 0/(800), 5/(200), 20/(800), 80/(3200)
3 month toxicity in rats	0/(0), 0/(4000), 5/(1000), 20/(2000), 80/(4000)
6 month toxicity in rats	0/(0), 0/(800), 5/(200), 20/(800), 30/(0)
3 (+1)* month toxicity in dogs	0/(500), 5/(300), 10/(400), 20/(500)
12 month toxicity in dogs	0/(0), 0/(800), 5/(200), 20/(800), 20/(0)

* +1 month of recovery

In the studies performed with itraconazole/(HP-β-CD) in mice, rats and dogs, the itraconazole dose of 5 mg/kg body weight was virtually not toxic. In rats, the only effects observed were, as expected from the toxicological profile of itraconazole, slightly increased serum cholesterol and phospholipid-levels, and minimal histological changes of the adrenal cortex (swelling), but without any cytopathological changes. In dogs, slight histological changes of the mononuclear

phagocytosing system (MPS) mainly consisting of an increase in foamy macrophages and adaptive changes in the urinary tract (swelling and vacuolation of epithelial cells in the renal pelvis and the urinary bladder) were the only effects observed, and they were mainly attributable to HP-β-CD.

In mice, dosing at 20/(800) and 80/(3200) mg/kg for 3 months resulted in slight to more pronounced toxicity. Serum aspartate and alanine aminotransferase levels were elevated, and at 80/(3200) mg/kg, associated with histological liver changes (eosinophilic aspect of hepatocytic cytoplasm and increase in individual cell necrosis). Histological examination further revealed modifications of the adrenal cortex (swelling) at 80/(3200) mg/kg bwt. In addition, HP-β-CD-related adaptive changes of the urinary tract were noted at 20/(800) and 80/(3200) mg/kg bwt.

In rats dosed for 3 months, 20/(2000) and 80/(4000) mg/kg bwt were moderately toxic doses. At these doses, target organs or tissues were similar to those observed with itraconazole alone, i.e. the adrenal cortex, the liver, the MPS, and the ovaries. Increased serum cholesterol and phospholipid-levels were also observed. Changes related to the HP-β-CD-vehicle were slightly decreased hematocrit and hemoglobin, a slightly lowered number of red blood cells, and adaptive changes of urinary bladder and renal pelvis.

Dosing in rats for 6 months at 20/(800) mg/kg and at 30/(0) mg/kg, a dose of itraconazole in PEG resulting in a similar systemic exposure, revealed toxicity mainly characterized by some altered blood and serum variables, and histological changes in MPS, liver and adrenal cortex. HP-β-CD-related effects in the 20/(800) and the 0/(800) mg/kg dosed groups were limited to histological changes in urinary tract and to an increased pancreas weight, but without apparent histological changes.

In dogs dosed for 3 months, itraconazole-related toxicity at 10/(400) and 20/(500) mg/kg bwt was confined to a slightly decreased body weight gain, some altered blood and serum variables, a slightly increased adrenal weight and foci of foamy cells in the lungs. The latter finding was also seen in the 0/(500)-vehicle dosed group, indicating that it is at least partially related to HP-β-CD.

Oral administration of HP-β-CD further led to slightly decreased hematocrit and hemoglobin and a slightly lowered number of red blood cells. After 1 month of recovery, the changed parameters in the 0/(500) and 20/(500) mg/kg dosed groups showed good reversibility.

Repeated dosing at 20/(800) or 20/(0) mg/kg for 12 months mainly produced reduced body weight gain and some changed blood and serum variables. At these doses, histological examination revealed itraconazole-related effects on the MPS and the adrenal cortex. Apart from transient softening of the stools and adaptive urinary tract changes, no other HP-β-CD-related effects were present.

Reproduction and Teratology

Segment I Reproduction Studies

Itraconazole was administered orally by gavage to groups of 24 male and 24 female rats in a segment I study, to assess its effects on male and female fertility. The dose levels studied were 10, 40 and 160 mg/kg/day, which were administered to males (minimum 60 days, prior to mating) and females (14 days prior to mating and a further 8 days during pregnancy). No adverse effects were found in the 10 mg/kg/day groups. There were no effects on fertility in the 40 mg/kg/day groups, but parental toxicity was present.

In the 160 mg/kg/day groups, parental toxicity including deaths occurred (2 males, 16 females). In the few surviving females of the 160 mg/kg/day group, pregnancy rates decreased and resorption rates increased, whereas other fertility parameters such as copulation index, number of corpora lutea, and the number of implantations per pregnant rat were normal. It was concluded that itraconazole had no primary effect on male or female fertility and that any adverse effects on fertility were secondary to the general toxicity seen at a partially lethal level of 160 mg/kg/day. No teratogenic effects were present in this study.

Segment II Reproduction Studies

In rats, itraconazole was administered by gavage (2 studies) and admixed with the diet. The dose levels in all rat studies were 10, 40 and 160 mg/kg/day. In the diet study, where itraconazole was administered to groups of 20 female rats from day 6 through day 15 of pregnancy, maternal toxicity and embryotoxicity were found at 40 and 160 mg/kg/day (100% resorption at 160 mg/kg/day). Teratogenic effects (major skeletal defects or abnormalities secondary to skeletal defects) were present in the offspring of the 40 mg/kg/day females. There were no fetuses of the 160 mg/kg/day dams available.

When itraconazole was administered via gavage to groups of 36 females (from day 8 through day 18 of pregnancy) in one study and groups of approximately 20 females (from day 6 through day 15 of pregnancy) in another study, maternal toxicity, embryotoxicity and teratologic changes were observed at 160 mg/kg/day. The only effect noted in the 40 mg/kg/day group was a slightly lowered pup weight in one of the two studies.

In a segment II rabbit study, the dose levels were 5 (17 females), 20 (15 females) and 80 (16 females) mg/kg/day administered by gavage from day 6 through day 18 of pregnancy. Reduced implantation was found in the 20 mg/kg/day dams but this observation is a predosing effect. In this study no embryotoxicity or teratogenicity was present. A second study was performed with the clinical pellet formulation. Doses administered to groups of 15 female rabbits by gavage were 25, 50 and 100 mg/kg/day from day 6 through day 18 of pregnancy. Slight maternal toxicity was characterized by decreased food consumption during and after dosing of 50 and 100 mg/kg/day. Itraconazole did not produce embryotoxic or teratogenic effects.

Two segment II reproduction studies were also conducted in mice, where itraconazole was administered by gavage from days 6 through 16 of pregnancy. The dose levels were 10, 40 and 160 mg/kg/day in the first study (groups of 24 dosed females) and 40, 80 and 160 mg/kg/day (groups of 30 dosed females) in the second. No adverse effects were found in the dams or fetuses of dams receiving 10 or 40 mg/kg/day. In the 80 and 160 mg/kg/day groups a few malformations (mainly encephaloceles and/or macroglossia) were found. A dose level of 160 mg/kg/day produced both maternal toxicity and embryotoxicity.

In a special segment II teratogenicity study in groups of 10 dosed female rats, it was shown that the embryotoxicity and teratogenicity seen after itraconazole at 160 mg/kg could be reduced by simultaneous administration of arachidonic acid. This protective effect of arachidonic acid is similar to what is known for non-steroidal and steroidal anti-inflammatory drugs. Since itraconazole did not show any relevant in vitro inhibitory activity on the target enzymes of the arachidonic acid pathway, an indirect, adrenal-mediated mechanism was proposed.

To evaluate this hypothesis, adrenalectomy was performed at day 4 of pregnancy in pregnant rats. Adrenalectomy resulted in a reduction of the embryotoxic and teratogenic effects of itraconazole dosed at 40 mg/kg. The data indicate that the adrenal effects seen at high dose levels of itraconazole are, at least partially, responsible for the adverse itraconazole effects on the progeny of pregnant rats.

Segment III Reproduction Studies
Perinatal and postnatal effects were studied in groups of 24 female rats in a segment III study. Itraconazole was administered via gavage at the rates of 5, 20 and 80 mg/kg/day from day 18 of pregnancy through a 3-week lactation period. There were no adverse effects at 5 or 20 mg/kg/day whereas maternal toxicity only was present at the dose level of 80 mg/kg/day. Except for a marginal effect on pup weight at 80 mg/kg, no embryotoxic or teratogenic or any other adverse effects were noticed in the offspring. In a subsequent, second generation study, no adverse effects on reproduction were noted in rats derived from dams (groups of 10 females) dosed up to 80 mg/kg.

Mutagenicity
Itraconazole was studied for mutagenic potential by the *Salmonella typhimurium* microsomal activation (Ames test), *Drosophila* recessive lethal mutation (*Drosophila melanogaster*), micronucleus formation (male and female rats), dominant lethal mutation (male and female mice), mouse lymphoma L5178Y test system and chromosome aberration (human lymphocytes). No mutagenic potential was demonstrated with any of these tests.

Carcinogenicity
Itraconazole was administered in the diet for 23 months to groups of 50 male and 50 female mice and for 24 months to groups of 50 male and 50 female rats in order to evaluate its carcinogenic potential.

In mice, itraconazole showed no evidence of carcinogenicity potential at oral dosage levels up to 80 mg/kg/day (approximately 10x the maximum recommended human dose (MRHD)).

However, female mice receiving 80 mg/kg/day displayed a temporary body weight decrease and an increased incidence of adrenal pigmentation.

Female rats treated with itraconazole at 50 mg/kg/day (6.25xMRHD), had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increased incidence in this study was not statistically significant. Male rats treated with 25 mg/kg/day (3.1xMRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcoma may have been a consequence of chronic inflammatory reaction of the connective tissue related to a rat-specific response of hypercholesterolemia, which was not observed in dogs or humans.

Hydroxypropyl-β-Cyclodextrin (HP-β-CD)
HP-β-CD is a new carrier molecule designed to enhance oral absorption and exposure to drugs. Chemically, it is a cyclic oligosaccharide built up from 7 glucopyranose units with 4.06 to 5.11 hydroxypropyl groups per molecule of cyclodextrin.

Pharmacology

Pharmacodynamic studies have shown that HP-β-CD has no intrinsic in vivo pharmacological activities that might hinder its presence in the clinical formulation of itraconazole oral solution. No interactions between HP-β-CD and drugs are expected from either a pharmacodynamic or a metabolic point of view.

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.

The pharmacokinetics of HP-β-CD after both intravenous and oral administration are similar in experimental animals and man. Intravenously dosed HP-β-CD is cleared very rapidly from the plasma, mainly by renal excretion of the intact compound. In animals, the tissue distribution is limited, and highest concentrations are measured in the urinary tract. The systemic absorption after oral administration of intact HP-β-CD is low. HP-β-CD is excreted for 50% - 62% of the dose as the intact compound in the feces. The bulk of the remaining part is metabolized by the intestinal microflora, and the absorption and tissue distribution of the biodegradation products are limited too. After oral dosing, the gastrointestinal tissues show the highest exposure to intact HP-β-CD as well as its biodegraded products. In view of the limited systemic absorption of HP-β-CD after oral administration, a stimulant effect on intestinal secretion and motility after high oral doses from 1500 mg/kg bwt onwards can be expected.

Toxicology

Single dose toxicity studies in mice, rats and dogs indicate a wide safety margin after oral and intravenous administration of HP-β-CD. In the (sub) chronic toxicity studies, most effects were of an adaptive nature (histological changes in the urinary tract, softening of feces, activation of the MPS) and showed good reversibility. Slight, reversible liver changes occurred at doses of about 30 times the proposed human dose of HP-β-CD in the itraconazole oral solution.

Oral treatment of juvenile Beagle dogs with HP-β-CD at 1200 mg/kg for a period of up to 13 weeks with a 4-week recovery period was clinically well tolerated with no effects noted when compared to control animals at laboratory or histopathology examination.

Mutagenicity

The chemical structure of HP-β-CD does not raise suspicion for genotoxic activity. Tests on DNA-damage, gene mutations and chromosome aberrations in vitro and in vivo did not reveal any genotoxic activity of HP-β-CD.

Carcinogenicity

In a rat carcinogenicity study, an increased incidence of neoplasms in the large intestine and in the exocrine pancreas was seen. The slightly higher incidence of adenocarcinomas in the large intestine was observed at 5000 mg/kg. The increased incidence was linked to the hypertrophic/ hyperplastic and inflammatory changes in the colonic mucosa brought about by the HP-β-CD-induced increased osmotic forces. There is no evidence of HP-β-CD per se exerting a tumorigenic effect on the large intestine. Hyperplasia and neoplasia of the exocrine pancreas, related to the mitogenic action of CCK, were only seen in those studies where HP-β-CD was given orally to rats. The clinical relevance of these findings is unknown.

In addition, HP-β-CD was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months. The likely mechanism is that oral administration of HP-β-CD resulted in a cholecystokinin (CCK)-mediated increase in hyperplasia of the acinar cells in the exocrine pancreas. This rat-specific finding was not observed in the mouse carcinogenicity study at doses 500, 2000 or 5000 mg/kg/day for 22-23 months.

This finding was also not observed in the chronic administration of HP-β-CD for 12 months to dogs (up to 2000 mg/kg bwt with eight dogs in each group) or to female cynomolgus monkeys for 2 years (800/400 mg/kg bwt, 13 monkeys per group) which did not cause hyperplastic/ neoplastic pancreatic changes.

Reproduction and Teratology

HP-β-CD has no antifertile, no direct embryotoxic and no teratogenic effect.

REFERENCES

1. Blatchford NR. Treatment of oral candidosis with itraconazole: a review. 2nd International Symposium on Itraconazole, Antwerp, Belgium, June 22-23, 1989. Journal of the American Academy of Dermatology 1990; 23(3)(Part 2):565-567.
2. Borgers M, Van de Ven MA. Mode of action of itraconazole: morphological aspects. Mycoses 1989; 32(Suppl 1):53-60.
3. Cauwenbergh G, De Doncker P, Stoops K, De Dier A, Goyvaerts H, Schuermans V. Itraconazole in the treatment of human mycoses: Review of three years of clinical experience. Reviews of Infectious Diseases 1987;9(Suppl 1):S146-S152.
4. Dupont B, Drouhet E. Early experience with itraconazole in vitro and in patients: pharmacokinetic studies and clinical results. Reviews of Infectious Diseases 1978;9: S71-76.
5. Grant SM, Clissold SP. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in superficial and systemic mycoses. Drugs 1989; 37:310-344.
6. Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn JG. Pharmacokinetics of itraconazole following oral administration to normal volunteers. Antimicrobial Agents and Chemotherapy 1988;32(9):1310-1313.
7. Heykants J, Michiels M, Meuldermans W, et al. The pharmacokinetics of itraconazole in animals and man: an overview. In: R.A. Fromtling, J.R. ed. Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents. Prous Science Publishers, S.A., 1987; 223-249.
8. Heykants J, Van Peer A, Van de Velde V, et al. The clinical pharmacokinetics of itraconazole: an overview. Mycoses 1989; 32(Suppl 1):67-87.
9. Moreno F, Hardin TC, Rinaldi MG, Graybill JR. Itraconazole-didanosine excipient interaction. Journal of the American Medical Association 1993; 269:1508.
10. Phillips P, Zemcov J, Mahmood W, et al. Itraconazole cyclodextrin solution for fluconazole-refractory oropharyngeal candidiasis in AIDS: correlation of clinical response with in vitro susceptibility. AIDS 1996; 10:1369-1376.
11. Restrepo A, Gonzalez A, Gomez I, Arango M, De Bedout C. Treatment of chromoblastomycosis with itraconazole. First International Conference on Drug Research in Immunologic and Infectious Diseases: Antifungal Drugs: Synthesis, Preclinical and Clinical Evaluation, New York, October 8-10, 1987. Annals of the New York Academy of Sciences 1988; 544:504-516.
12. Smith DE, Midgely J, Allan M, Connolly GM, Gazzard BG. Itraconazole versus ketoconazole in the treatment of oral and oesophageal candidosis in patients infected with HIV. AIDS 1991; 5:1367-1371.
13. Tucker RM, Williams PL, Arathoon EG, Stevens DA. Treatment of mycoses with itraconazole. Annals of the New York Academy of Sciences 1988;544:451-470.
14. Van Cauteren H, Coussement W, Vandenberghe J, Herin V, Vanparys PH, Marsboom R: The toxicological properties of itraconazole. In: R.A. Fromtling, J.R. ed. Recent Trends

in the Discovery, Development and Evaluation of Antifungal Agents. Prous Science Publishers, S.A. 1987; 263-271.

15. Van Cutsem J. Oral, topical and parenteral antifungal treatment with itraconazole in normal and in immunocompromised animals. Mycoses 1989; 32(Suppl 1):14-35.
16. Van Cutsem J. The in-vitro antifungal spectrum of itraconazole. Mycoses 1989; 32 (Suppl 1):7-14.
17. Van Cutsem J, Van Gerven F, Janssen PAJ. The in vitro and in vivo antifungal activity of itraconazole. In: R.A. Fromtling J.R., et al. eds. Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents. Telesymposia proceedings. Prous Science Publishers, Barcelona, 1987.
18. Vanden Bossche H, Marichal P, Gorrens J, et al. Biochemical approaches to selective antifungal activity. Focus on azole antifungals. Mycoses 1989; 32(Suppl 1):35-53.
19. Van de Velde Vera JS, Van Peer Achiel P, Heykants Joseph JP, et al. Effect of Food on the Pharmacokinetics of a New Hydroxypropyl-β-Cyclodextrin Formulation of Itraconazole. Pharmacotherapy 1996; 16(3):424-428.
20. Warnock DW, Turner A, Burke J. Comparison of high performance liquid chromatographic and microbiological methods for determination of itraconazole. Antimicrobial Agents and Chemotherapy 1988; 21:93-100.
21. Product Monograph - SPORANOX® (Itraconazole oral solution) 10 mg/mL, Janssen Inc., Control No. 220658; Date of Revision: December 5, 2018.

PART III: CONSUMER INFORMATION
PrODAN ITRACONAZOLE
Itraconazole Oral Solution, BP

This leaflet is Part III of a three-part "Product Monograph" published when **ODAN ITRACONAZOLE** oral solution was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **ODAN ITRACONAZOLE** oral solution. Contact your doctor or pharmacist if you have any questions about the drug.

This information is for patients who have been prescribed **ODAN ITRACONAZOLE** oral solution for treatment of fungal infections of the mouth and throat. This information does not take the place of discussion between you and your doctor. Only your doctor can decide if **ODAN ITRACONAZOLE** treatment is right for you.

ABOUT THIS MEDICATION

What the medication is used for:

ODAN ITRACONAZOLE is a prescription medication used to treat fungal infections of the mouth and throat in adult HIV-positive patients or other patients with a lowered immune system.

This Consumer Information discusses only the oral solution form of **ODAN ITRACONAZOLE**. You will receive the oral solution in a glass bottle, containing 150 mL of solution (10 mg itraconazole per millilitre solution), along with a measuring cup.

What it does:

ODAN ITRACONAZOLE goes into your bloodstream and travels to the area of the infection.

When it should not be used:

- if you have congestive heart failure, **ODAN ITRACONAZOLE** could make it worse. If your doctor decides that you need **ODAN ITRACONAZOLE**, be sure to get immediate medical help if you experience signs of heart failure (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**)
- if you are taking certain medications (see **INTERACTIONS WITH THIS MEDICATION**)
- if you have had an allergic reaction to itraconazole or any of the other ingredients in **ODAN ITRACONAZOLE** oral solution (see **What the nonmedicinal ingredients are**)

What the medicinal ingredient is:

The medicinal ingredient in oral solution is itraconazole. One full measuring cup contains 30 millilitres of solution, corresponding to 300 milligrams of itraconazole.

What the nonmedicinal ingredients are:

ODAN ITRACONAZOLE oral solution contains: hydroxypropyl-β-cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour, sodium saccharin, sodium hydroxide and purified water.

What dosage forms it comes in:

Oral Solution 10 mg / mL

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Liver toxicity (see **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**)
- Heart problems (see **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**)
- Drug interactions (see **INTERACTIONS WITH THIS MEDICATION**)

ODAN ITRACONAZOLE treatment is not for everyone. Your doctor will decide if **ODAN ITRACONAZOLE** is the right treatment for you. Some patients should not take **ODAN ITRACONAZOLE** oral solution because they may have certain health problems or may be taking certain medications that could lead to serious or life-threatening medical problems.

Tell your doctor about any other medical conditions you have had, especially heart, lung, liver or kidney conditions.

- If you have a liver problem, your dose of **ODAN ITRACONAZOLE** oral solution may have to be adjusted;
- If you have a kidney disorder, your dose of **ODAN ITRACONAZOLE** oral solution may have to be adjusted.

Also tell your doctor and pharmacist the name of all the prescription and non-prescription medications you are taking, including dietary supplements and herbal remedies.

BEFORE you use **ODAN ITRACONAZOLE** oral solution, let your doctor or pharmacist know if:

- you have elevated or abnormal liver enzymes or active liver disease, or have experienced liver toxicity with other drugs;
- you have or have had heart disease, including congestive heart failure;
- you have cystic fibrosis;
- you have ever had an allergic reaction to itraconazole or any of the other ingredients in **ODAN ITRACONAZOLE** oral solution.

ODAN ITRACONAZOLE oral solution can sometimes cause dizziness, blurred/double vision or hearing loss. If you have these symptoms, do not drive or use machines.

Since scientific information on the use of **ODAN ITRACONAZOLE** oral solution in children is limited, it is not recommended for use in children.

Pregnancy

Do not take **ODAN ITRACONAZOLE** oral solution if you are pregnant (unless your doctor knows you are pregnant and decides you need **ODAN ITRACONAZOLE)** or planning to become pregnant within 2 months after you have finished your treatment. Serious birth defects have been seen in animals and women treated with itraconazole during pregnancy. It is not known whether itraconazole caused these defects. A reliable form of barrier contraception must always be used even if you or your partner are using other methods of contraception such as the pill or other hormonal therapy (e.g. implants,

injections). **ODAN ITRACONAZOLE** may remain in your blood for a time after therapy is stopped. Therefore, you should continue use of a reliable form of contraception for 2 months after stopping treatment with **ODAN ITRACONAZOLE** .

Breast-feeding

Do not take **ODAN ITRACONAZOLE** oral solution if you are breast-feeding or discontinue nursing if you are taking **ODAN ITRACONAZOLE**. **ODAN ITRACONAZOLE** is found in human breast milk.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist what medications you are currently taking. In particular, some medications must not be taken at the same time, and if certain medications are taken at the same time, changes need to be made (to the dose, for example). A wide variety of drugs may interact with **ODAN ITRACONAZOLE** oral solution.

Never take ODAN ITRACONAZOLE oral solution if you are taking any of the following medications:

- boosted asunaprevir to treat Hepatitis C Virus
- eplerenone, felodipine, ivabradine, ranolazine used to treat angina (crushing chest pain) or high blood pressure
- ticagrelor used to slow down blood clotting
- eletriptan used to treat migraine headaches
- lomitapide, lovastatin, simvastatin which lower cholesterol
- triazolam, sleeping pills
- disopyramide, dronedarone, quinidine, used to treat irregular heart beat rhythms
- lurasidone, pimozide used for psychotic disorders
- methadone for severe pain or to manage addiction
- irinotecan, an anti-cancer drug
- dihydroergotamine or ergotamine (called ergot alkaloids) used in the treatment of migraine headaches
- ergometrine (ergonovine) (called ergot alkaloids) used to control bleeding and maintain uterine contraction after child birth
- domperidone used to treat nausea and vomiting
- naloxegol; to treat constipation caused by taking opioid painkillers
- eliglustat to treat Gaucher disease type 1 (GD1)

If you have kidney or liver impairment, never take ODAN ITRACONAZOLE oral solution while taking any of the following medications:

- colchicine, used to treat gout
- fesoterodine or solifenacin when used to control irritated urinary bladder

Wait at least 2 weeks after stopping **ODAN ITRACONAZOLE** oral solution before taking any of these medications.

Medications that can decrease the action of ODAN ITRACONAZOLE oral solution and are not recommended unless your doctor feels it is necessary:

- carbamazepine, phenobarbital, phenytoin used to treat epilepsy
- isoniazid, rifabutin, rifampicin used to treat tuberculosis
- efavirenz, nevirapine used to treat HIV/AIDS.

You should therefore always tell your doctor if you are using any of these products so that the appropriate measures can be taken.

Wait at least 2 weeks after stopping these medications before taking **ODAN ITRACONAZOLE** oral solution.

Medications not recommended unless your doctor feels it is necessary:

- axitinib, bosutinib, cabazitaxel, ceritinib, cobimetinib, crizotinib, dabrafenib, dasatinib, docetaxel, ibrutinib, lapatinib, nilotinib, olaparib, pazopanib, regorafenib, sunitinib, trabectedin, trastuzumab emtansine, vinca alkaloids used in the treatment of cancer
- riociguat, sildenafil, tadalafil, when used to treat pulmonary hypertension (increased blood pressure in the blood vessels in the lungs)
- everolimus, rapamycin (also known as sirolimus), usually given after an organ transplant
- conivaptan, tolvaptan, to treat low blood sodium
- apixaban, rivaroxaban to slow down blood clotting
- alfuzosin, silodosin to treat Benign Prostatic enlargement
- aliskiren to treat hypertension
- carbamazepine to treat epilepsy
- colchicine to treat gout
- darifenacin to treat urinary incontinence
- fentanyl a strong medication to treat pain
- vorapaxar used to treat heart attacks or strokes
- salmeterol to improve breathing
- simeprevir to treat Hepatitis C Virus
- tamsulosin to treat male urinary incontinence
- vardenafil to treat erectile dysfunction
- *Saccharomyces boulardii* to treat diarrhea
- lumacaftor/ ivacaftor to treat Cystic Fibrosis.

Wait at least 2 weeks after stopping these medications before taking **ODAN ITRACONAZOLE** oral solution.

Medications that may require a dose change (for either ODAN ITRACONAZOLE oral solution or the other medication):

- ciprofloxacin, clarithromycin, erythromycin, antibiotics
- bosentan, digoxin, nadolol and certain calcium-channel blockers including verapamil; that act on the heart or blood vessels
- guanfacine to treat Attention Deficit Hyperactivity Disorder
- diltiazem to treat hypertension
- cilostazol, coumarins (e.g., warfarin), dabigatran; that slow down blood clotting
- budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone (medications given by mouth, injection or inhalation for conditions such as inflammations, asthma, and allergies)
- cyclosporine, tacrolimus, temsirolimus, which are usually given after an organ transplant
- cobicistat, boosted elvitegravir, tenofovir disoproxil fumarate (TDF), maraviroc, and protease inhibitors: indinavir, ritonavir, boosted darunavir, ritonavir-boosted fosamprenavir, saquinavir; used in the treatment of HIV/AIDS
- dienogest, ulipristal used as contraceptives
- daclatasvir, telaprevir, glecaprevir/pibrentasvir; elbasvir/grazoprevir used in the treatment of Hepatitis C Virus
- bortezomib, brentuximab vedotin, busulfan, erlotinib, gefitinib, idelalisib, imatinib, ixabepilone, nintedanib,

ponatinib, ruxolitinib, vandetanib; used in the treatment of cancer
- alprazolam, brotizolam, buspirone, midazolam IV, perospirone, ramelteon for anxiety or to help you sleep (tranquillizer)
- alfentanil, buprenorphine, oxycodone, sufentanil; strong medications to treat pain
- repaglinide, saxagliptin to treat diabetes
- aripiprazole, haloperidol, quetiapine, risperidone to treat psychosis
- zopiclone to treat insomnia
- aprepitant to treat nausea and vomiting during cancer treatment
- loperamide to treat diarrhea
- fesoterodine, imidafenacin, oxybutynin, solifenacin, tolterodine; to control irritated urinary bladder
- dutasteride to treat Benign Prostatic enlargement
- sildenafil, tadalafil to treat erectile dysfunction
- praziquantel; to treat fluke and tapeworms
- bilastine, ebastine, rupatadine; for allergy
- reboxetine, venlafaxine; to treat depression and anxiety
- quinine to treat malaria
- atorvastatin to lower cholesterol
- meloxicam to treat joint inflammation and pain
- cinacalcet; to treat an over active parathyroid
- mozavaptan to treat low blood sodium
- alitretinoin (oral formulation), to treat eczema
- cabergoline to treat Parkinsons Disease
- cannabinoids; to treat nausea and vomiting, weight loss for patients with immune system problems and muscle spasms in patients with Multiple Sclerosis
- ivacaftor to treat Cystic Fibrosis
- galantamine; to treat Alzheimer's disease.

Always tell your doctor, nurse or pharmacist if you are taking any other medications, either prescription or over-the- counter, herbal medications or natural health products.

PROPER USE OF THIS MEDICATION

You should always take **ODAN ITRACONAZOLE** oral solution without food. You should not eat or drink for one hour after taking Odan Itraconazole oral solution.

Do not use **ODAN ITRACONAZOLE** oral solution for a condition for which it was not prescribed. Do not give **ODAN ITRACONAZOLE** oral solution to other people, even if they have the same symptoms you have. It may harm them

Do not switch to itraconazole capsules without talking to your doctor.

Usual dose:
Your doctor will decide the right dose for you. Depending on your infection, you will take **ODAN ITRACONAZOLE** oral solution once or twice a day for as long as prescribed by your doctor.

Use the dosing cup provided in your **ODAN ITRACONAZOLE** package to accurately measure the amount of solution needed.

ODAN ITRACONAZOLE oral solution should be poured into the cup containing markings which indicate dosing amounts (5 mL to 30 mL) in increments of 5 mL. You should swish the solution around in your mouth for approximately 20 seconds before swallowing it, and avoid rinsing your mouth after taking it.

Overdose:

If you think you have taken too much ODAN ITRACONAZOLE, contact your healthcare professional, hospital emergency department, or regional P oison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you forget to take, or miss doses of **ODAN ITRACONAZOLE** oral solution ask your doctor what you should do with the missed doses. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects that cause people to stop treatment either for a short time or completely include: skin rash, high triglyceride test results (fats in your blood), high liver test results, and digestive system problems (such as nausea, bloating, and diarrhea).

Other side effects that may occur with **ODAN ITRACONAZOLE** treatment include upset stomach, vomiting, abdominal pain, constipation or excess gas in stomach, cough, fluid in the lungs, altered voice, inflammation of the sinuses, inflammation of the nose, upper respiratory tract infection, headache, dizziness, menstrual disorders, erectile dysfunction, confusion, tremor, sleepiness, fatigue, chills, muscle weakness or pain, painful joints, pain, chest pain, swelling, generalized swelling, unpleasant taste, hair loss, inflammation of the pancreas, fever, excessive sweating may also occur.

Report any side effects to your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect *The following side effects are all uncommon:*	Talk with your doctor or pharmacist immediately		Stop taking drug and call your doctor or pharmacist immediately
	Only if severe	In all cases	
Heart Problems			
• Develop shortness of breath		✓	
• Unusual swelling of feet, ankles or legs		✓	
• Sudden weight gain		✓	
• Unusually tired		✓	
• Cough up white or pink phlegm		✓	
• Unusual fast heartbeats		✓	
• Begin to wake up at night		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect *The following side effects are all uncommon:*	Talk with your doctor or pharmacist immediately		Stop taking drug and call your doctor or pharmacist immediately
	Only if severe	In all cases	
Liver Problems			
• Unusually tired			✓
• Loss of appetite			✓
• Nausea			✓
• Abdominal pain			✓
• Vomiting			✓
• Yellow colour to skin or eyes			✓
• Dark-coloured urine			✓
• Pale stools			✓
Nerve Problems			
• Tingling			✓
• Numbness			✓
• Reduced sense of touch			✓
• Weakness in the limbs			✓
• Pain			✓
• Pins and needles			✓
• Prickling or burning			✓
Hypersensitivity			
• Skin rash			✓
• Itching			✓
• Hives			✓
• Difficulty breathing or shortness of breath and/or			✓
• Swelling of the face			✓
Severe Skin Disorder			
• Widespread rash with peeling skin and blisters in the mouth, eyes and genitals or			✓
• Rash with small pustules or blisters			✓
Other			
• Blurry or double vision		✓	
• Ringing in ears		✓	
• Oversensitivity to sunlight			✓
• Loss of ability to control urine or urinate much more than usual		✓	
• Hearing loss symptoms[a]			✓

[a] Cases of temporary or permanent hearing loss have been reported in patients taking Itraconazole.

*This is not a complete list of side effects. For any unexpected effects while taking **ODAN ITRACONAZOLE** oral solution, contact your doctor or pharmacist.*

HOW TO STORE IT

Keep all medications, including **ODAN ITRACONAZOLE** oral solution, out of the reach and sight of children.

Store **ODAN ITRACONAZOLE** oral solution at room temperature (15°C - 30°C). This medication can be kept for only a limited time.
Discard any remaining unused **ODAN ITRACONAZOLE** oral solution three months after opening the bottle.

REPORTING SIDE EFFECTS

You can report any suspected side effectseffects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse reaction reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html for more information on how to report online, by mail or by fax
- Call toll-free at 1-866-234-2345

***NOTE:** Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

If you want more information about **ODAN ITRACONAZOLE**:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) or by contacting the sponsor, Odan Laboratories Ltd. at 1-888-666-6326.

This leaflet was prepared by Odan Laboratories Ltd.
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