PRODUCT NAME
SPORANOX® ORAL SOLUTION

Generic Name/International Non-Proprietary Name
Itraconazole

DOSAGE FORMS AND STRENGTHS
SPORANOX® oral solution is clear.
1 mL SPORANOX® oral solution contains 10 mg itraconazole.

For excipients, see *List of Excipients.*

CLINICAL INFORMATION

Indications
SPORANOX® oral solution is indicated:
- For the treatment of oral and/or esophageal candidosis in HIV-positive or other immunocompromised patients.
- As prophylaxis of deep fungal infections, in patients with hematological malignancy or undergoing bone marrow transplant, and who are expected to become neutropenic (i.e. < 500 cells/µL).
- For empiric therapy of febrile neutropenic patients with suspected systemic mycoses as follow-up therapy to SPORANOX® IV.

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

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

Treatment of oral candidosis
200 mg (2 measuring cups, i.e. 20 mL) per day in two intakes, or alternatively in one intake, for 1 week. If there is no response after 1 week, treatment should be continued for another week.

Treatment of esophageal candidosis
100 mg (1 measuring cup, i.e. 10 mL) daily for a minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg (2 measuring cups, i.e. 20 mL) per day may be used based on the clinical response of the patient.

Treatment of fluconazole resistant oral and/or esophageal candidosis
100 to 200 mg (1-2 measuring cups) twice daily for 2 weeks. If there is no response after 2 weeks, treatment should be continued for another 2 weeks. The 400 mg daily dose should not be used for longer than 14 days if there are no signs of improvement.

Prophylaxis of fungal infections
5 mg/kg per day administered in two intakes. In clinical trials, prophylaxis treatment was started immediately prior to the cytostatic treatment and generally one week before transplant procedure. Treatment was continued until recovery of neutrophils (i.e. > 1000 cells/µL).

Empiric therapy of febrile neutropenic patients with suspected systemic mycoses
Treatment should be started with SPORANOX® IV. The recommended dose of SPORANOX® IV is 200 mg b.i.d. for four doses, followed by 200 mg once daily for up to 14 days. Each intravenous dose should be infused over 1 hour. Treatment should be continued with SPORANOX® oral solution 200 mg (20 mL) b.i.d. until resolution of clinically significant neutropenia. The safety and efficacy of SPORANOX® use exceeding 28 days in empiric therapy of febrile patients with suspected systemic mycoses is not known.

Special populations

Pediatrics
Clinical data on the use of SPORANOX® oral solution in pediatric patients are limited. The use of SPORANOX® oral solution in pediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks (see *Warnings and Precautions*).

Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes. The incidence of adverse events such as diarrhea, abdominal pain, vomiting, fever, rash and mucositis was higher than in adults. However, it is not clear to what extent this is attributable to SPORANOX® oral solution or the chemotherapy.

Elderly
Clinical data on the use of SPORANOX® oral solution in elderly patients are limited. It is advised to use SPORANOX® oral solution in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see *Warnings and Precautions*).

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 *Pharmacokinetic Properties - Special populations, Hepatic impairment*).

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 *Pharmacokinetic Properties - Special populations, Renal impairment*).

Contraindications

- SPORANOX® oral solution is contraindicated in patients with known hypersensitivity to itraconazole or to any of the excipients.
- Co-administration of a number of CYP3A4 substrates is contraindicated with SPORANOX® oral solution. 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. 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. Some specific examples are listed in *Interactions.*
- SPORANOX® 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 *Warnings and Precautions*).
- SPORANOX® oral solution must not be used during pregnancy (except for life-threatening cases) (see *Pregnancy, Breast-feeding and Fertility*).

Women of childbearing potential taking SPORANOX® oral solution should use contraceptive precautions. Highly effective contraception should be continued until the menstrual period following the end of SPORANOX® oral solution therapy.

Warnings and Precautions

Cardiac effects

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

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

SPORANOX® should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen, (e.g., total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, SPORANOX® should be discontinued.

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 co-administering itraconazole and calcium channel blockers due to an increased risk of CHF.

Interaction potential

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

Cross-hypersensitivity

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

Neuropathy

If neuropathy occurs that may be attributable to SPORANOX® oral solution, the treatment should be discontinued.

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.

Cross-resistance

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

Interchangeability

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

Hepatic effects

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

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population. It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolized by CYP3A4.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with SPORANOX® is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring should be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications.

(See *Pharmacokinetic Properties - Special populations, Hepatic 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 bid. 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 SPORANOX® oral solution, consideration should be given to switching to SPORANOX® IV or to alternative therapy.

Pediatrics

Clinical data on the use of SPORANOX® oral solution in pediatric patients are limited. The use of SPORANOX® oral solution in pediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.

Elderly

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

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 *Pharmacokinetic Properties - Special populations, renal impairment*).

Treatment of severely neutropenic patients

SPORANOX® oral solution as treatment for oral and/or esophageal candidosis was not investigated in severely neutropenic patients. Due to the pharmacokinetic properties (see *Pharmacokinetic Properties*), SPORANOX® oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidosis.

Interactions

Itraconazole is a drug with a high interaction potential. The various types of interaction and associated general recommendations are described below. In addition, a table is provided listing examples of drugs that may interact with itraconazole, organized per drug family for easy reference.

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.

- ‘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

The list of examples of interacting drugs in the table below is not comprehensive and therefore the label 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. 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.

Examples of 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		
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].
Levacetylmethadol (levomethadyl)	Levacetylmethadol C_{max} (↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of levacetylmethadol-related adverse reactions, such as QT prolongation and TdP.
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.

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
Antiarrhythmics		
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.
Dofetilide	Dofetilide C_{max} (↑), AUC (↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of dofetilide-related adverse reactions, such as serious ventricular 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		
Bedaquiline	Bedaquiline C_{max} (↔), AUC (↑) during 2 weeks of bedaquiline q.d. dosing[a]	Not recommended, coadministration for more than 2 weeks at any time during bedaquiline dosing is not recommended: increased risk of bedaquiline-related adverse reactions[c].
Ciprofloxacin Erythromycin	Itraconazole C_{max} ↑, AUC ↑	Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
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.
Delamanid Trimetrexate	Delamanid conc. increase (extent unknown)[a,b] Trimetrexate conc increase (extent unknown)[a,b]	Use with caution, monitor for delamanid/trimetrexate adverse reactions[c], dose reduction of delamanid/trimetrexate 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

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
		reduced and increased risk of rifabutin-related adverse reactions[c].
Telithromycin	In healthy subjects: telithromycin C_{max} ↑, AUC ↑ In severe renal impairment: telithromycin AUC (↑↑)[a] In severe hepatic impairment: telithromycin conc. increase (extent unknown)[a,b]	Contraindicated in patients with severe renal or hepatic impairment during and for 2 weeks after treatment with itraconazole, Increased risk of telithromycin-related adverse reactions, such as hepatotoxicity, QT prolongation and TdPs[c]. Use with caution in other patients:, monitor for telithromycin adverse reactions, dose reduction of telithromycin may be necessary.
Anticoagulants and Antiplatelet Drugs		
Apixaban Edoxaban Rivaroxaban Vorapaxar	Apixaban C_{max} (↑), AUC (↑)[a] Edoxaban 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/edoxaban/rivaroxaban/ vorapaxar-related adverse reactions[c].
Coumarins (e.g., 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[c], dose reduction of coumarins/cilostazol may be necessary.
Dabigatran	Dabigatran C_{max} (↑↑), AUC (↑↑)[a]	Use with caution, monitor for dabigatran adverse reactions[c], dose reduction of dabigatran may be necessary.
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		
Repaglinide Saxagliptin	Repaglinide C_{max} ↑, AUC ↑ Saxagliptin C_{max} (↑↑), AUC (↑↑)[a]	Use with caution, monitor for repaglinide/saxagliptin adverse reactions[c], dose reduction of repaglinide/saxagliptin may be necessary.
Antihelminthics, antifungals and antiprotozoals		
Artemether-lumefantrine Quinine	Artemether C_{max} (↑↑), AUC (↑↑)[a] Lumefantrine C_{max} (↑), AUC (↑)[a] Quinine C_{max} ↔, AUC ↑	Use with caution, monitor for artemether-lumefantrine/quinine adverse reactions. Refer to the label for specific actions to be taken.

Examples of medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Halofantrine	Halofantrine conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of halofantrine-related adverse reactions, such as QT prolongation and fatal arrhythmias.
Isavuconazole	Isavuconazole C_{max} (↔), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of isavuconazole-related adverse reactions, such as hepatic adverse reactions, hypersensitivity reactions and embryo-fetal toxicity.
Praziquantel	Praziquantel C_{max} (↑↑), AUC (↑)[a]	Use with caution, monitor for praziquantel adverse reactions[c], dose reduction of praziquantel may be necessary.
Antihistamines		
Astemizole	Astemizole C_{max} (↑), AUC (↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of astemizole-related adverse reactions, such as QT prolongation, TdP and other ventricular arrhythmias.
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.
Mizolastine	Mizolastine C_{max} (↑), AUC (↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of mizolastine-related adverse reactions, such as QT prolongation.
Terfenadine	Terfenadine conc increase (extent unknown)[b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of terfenadine-related adverse reactions, such as QT prolongation, TdP and other ventricular arrhythmias.
Antimigraine Drugs		
Eletriptan	Eletriptan C_{max} (↑↑), AUC (↑↑↑)[a]	Use with caution, monitor for eletriptan adverse reactions[c], dose reduction of eletriptan may be necessary.
Ergot alkaloids (such as dihydroergotamine, ergometrine, ergotamine, methylergometrine)	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	Bortezomib AUC (↑)[a] Brentuximab vedotin AUC (↑)[a] Busulfan C_{max} ↑, AUC ↑	Use with caution, monitor for adverse reactions related to the antineoplastic drug[c],

Examples of medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Busulfan Erlotinib Gefitinib Imatinib Ixabepilone Nintedanib Panobinostat Pemigatinib Ponatinib Ruxolitinib Sonidegib Tretinoin (oral) Vandetanib	Erlotinib C_{max} (↑↑), AUC (↑)[a] Gefitinib C_{max} ↑, AUC ↑ Imatinib C_{max} (↑), AUC (↑)[a] Ixabepilone C_{max} (↔), AUC (↑)[a] Nintedanib C_{max} (↑), AUC (↑)[a] Panobinostat C_{max} (↑), AUC (↑)[a] Pemigatinib C_{max} ↑, AUC ↑ Ponatinib C_{max} (↑), AUC (↑)[a] Ruxolitinib C_{max} (↑), AUC (↑)[a] Sonidegib C_{max} (↑), AUC (↑↑)[a] Tretinoin C_{max} (↑), AUC (↑)[a] Vandetanib C_{max} ↔, AUC ↑	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.
Axitinib Bosutinib Cabazitaxel Cabozantinib Ceritinib Cobimetinib Crizotinib Dabrafenib Dasatinib Docetaxel Entrectinib Glasdegib Ibrutinib Lapatinib Nilotinib Olaparib Pazopanib Sunitinib Talazoparib Trabectedin Trastuzumab emtansine Vinca alkaloids	Axitinib C_{max} (↑), AUC (↑↑)[a] Bosutinib C_{max} (↑↑↑), AUC (↑↑↑)[a] Cabazitaxel C_{max} (↔), AUC (↔)[a] Cabozantinib 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] Entrectinib C_{max} ↑, AUC ↑ ↑ ↑ Glasdegib C_{max} (↑), AUC (↑ ↑)[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] Talazoparib C_{max} ↑, AUC ↑ Trabectedin C_{max} (↑), AUC (↑)[a] Trastuzumab emtansine 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 label 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

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
		as potentially life-threatening myelosuppression and diarrhea.
Mobocertinib	Mobocertinib C_{max} ↑↑, AUC ↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of mobocertinib-related adverse reactions[c].
Venetoclax	Venetoclax C_{max} (↑↑↑), AUC (↑↑↑)[a]	Contraindicated for chronic lymphocytic leukemia/small lymphocytic lymphoma patients during dose initiation/titration/ramp-up phase of venetoclax. Otherwise, not recommended during and for 2 weeks after treatment with itraconazole[c].
Antipsychotics, Anxiolytics and Hypnotics		
Alprazolam Aripiprazole Brotizolam Buspirone Cariprazine Haloperidol Midazolam (iv) Perospirone Quetiapine Ramelteon Risperidone Suvorexant Zopiclone	Alprazolam C_{max} ↔, AUC ↑↑ Aripiprazole C_{max} ↑, AUC ↑ Brotizolam C_{max} ↔, AUC ↑↑ Buspirone C_{max} ↑↑↑↑, AUC ↑↑↑↑ Cariprazine (↑↑)[a,b] 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] Suvorexant C_{max} (↑), AUC (↑↑)[a] 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.
Midazolam (oral)	Midazolam (oral) C_{max} ↑ to ↑↑, AUC ↑↑ to ↑↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of midazolam-related adverse reactions, such as respiratory depression, cardiac arrest, prolonged sedation and coma.
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.
Sertindole	Sertindole conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of sertindole-related adverse reactions, such as 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

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
		as seizures, respiratory depression, angioedema, apnea and coma.
Antivirals		
Asunaprevir Tenofovir disoproxil fumarate (TDF)	Asunaprevir C_{max} (↑↑↑), AUC (↑↑↑)[a] Tenofovir conc increase (extent unknown)[a,b]	Use with caution, however, refer to the label of the antiviral drug for specific actions to be taken.
Boceprevir	Boceprevir C_{max} (↑), AUC (↑↑)[a] Itraconazole conc increase (extent unknown)[a,b]	Use with caution, monitor for adverse reactions related to itraconazole and/or boceprevir[c], dose reduction of itraconazole may be necessary. Refer to the boceprevir label 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 Vaniprevir	Daclatasvir C_{max} (↑), AUC (↑↑)[a] Vaniprevir C_{max} (↑↑↑), AUC (↑↑↑)[a]	Use with caution, monitor for daclatasvir/vaniprevir adverse reactions[c], dose reduction of daclatasvir/vaniprevir may be necessary.
Darunavir (boosted) Fosamprenavir (ritonavir-boosted)	Ritonavir-boosted darunavir: itraconazole C_{max} (↑↑), AUC (↑↑)[a] Ritonavir-boosted fosamprenavir: itraconazole C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
Elvitegravir (boosted)	Ritonavir-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 label 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 label for specific actions to be taken.
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 label 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.

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
Ombitasvir/Paritaprevir/ Ritonavir with or without Dasabuvir	Itraconazole C_{max} (↑), AUC (↑↑)[a] Ombitasvir C_{max} (↔), AUC (↑)[a] Paritaprevir C_{max} (↑), AUC (↑↑)[a] Ritonavir C_{max} (↑), AUC (↑)[a] Dasabuvir C_{max} (↑), AUC (↑)[a]	Use with caution, monitor for adverse reactions related to itraconazole and/or the antivirals[c], dose reduction of itraconazole may be necessary. Refer to the label(s) of the coadministered drugs for specific actions to be taken.
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 label 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 label for specific actions to be taken.
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		
Bepridil	Bepridil conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of bepridil-related adverse reactions, such as new arrhythmias and TdP type ventricular tachycardia.
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 Lercanidipine Nisoldipine	Felodipine C_{max} ↑↑↑, AUC ↑↑↑ Lercanidipine AUC (↑↑↑↑)[a] Nisoldipine C_{max} (↑↑↑↑), AUC (↑↑↑↑)[a]	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, Misc		
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 Urological 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.

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
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 label 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.
Finerenone	Finerenone C_{max} (↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of finerenone-related adverse reactions[c].
Gastrointestinal Drugs		
Aprepitant Loperamide Netupitant	Aprepitant AUC (↑↑↑)[a] Loperamide C_{max} ↑↑, AUC ↑↑ Netupitant C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for aprepitant/loperamide/netupitant adverse reactions[c]. Dose reduction of aprepitant/loperamide/ may be necessary. Refer to the netupitant label for specific actions to be taken.
Cisapride	Cisapride conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of cisapride-related adverse reactions, such as serious cardiovascular events including QT prolongation, serious ventricular arrhythmias and TdP.
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.

Examples of medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Saccharomyces boulardii	*S. boulardii* colonization decrease (extent unknown)[a,b]	Not recommended during and for 2 weeks after treatment with itraconazole. S. boulardii efficacy may be reduced.
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. Increased risk of everolimus/ sirolimus-related adverse reactions[c].
Voclosporin	Voclosporin C_{max} (↑↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of voclosporin-related adverse reactions[c].
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.

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
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.
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		
Avanafil	Avanafil C_{max} (↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk avanafil-related adverse reactions, such as priapism, visual problems and sudden loss of hearing.
Dapoxetine	Dapoxetine C_{max} (↑), AUC (↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk for dapoxetine-related adverse reactions, such as orthostatic hypotension and ocular effects.
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 Udenafil	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 Udenafil C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for urologic drug adverse reactions[c], dose reduction of the urologic drug may be necessary; refer to the dutasteride label for specific actions to be taken. (For sildenafil and tadalafil, see also Cardiovascular Drugs, Miscellaneous).
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.

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
		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		
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[c], dose reduction of alitretinoin/ cabergoline/cannabinoids/cinacalcet may be necessary.
Valbenazine	Valbenazine C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for valbenazine-related adverse reactions[c], dose reduction of valbenazine is necessary.
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)

Examples of medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
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. Increased risk of ivacaftor-related adverse reactions[c].
Vasopressin Receptor Antagonists		
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 label for information on drug-related adverse reactions

Pediatric population

Interaction studies have only been performed in adults.

Pregnancy, Breast-feeding and Fertility

Pregnancy
SPORANOX® 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 (see *Contraindications*).

In animal studies itraconazole has shown reproduction toxicity (see *Non-Clinical Information*).

There is limited information on the use of SPORANOX® 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 SPORANOX® has not been established.

Epidemiological data on exposure to SPORANOX® during the first trimester of pregnancy – mostly in patients receiving short-term treatment for vulvovaginal candidosis – did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens. Itraconazole has been shown to cross the placenta in a rat model.

Women of childbearing potential
Women of childbearing potential taking SPORANOX® oral solution should use contraceptive precautions. Highly effective contraception should be continued until the menstrual period following the end of SPORANOX® therapy.

Breast-feeding
A very small amount of itraconazole is excreted in human milk. The expected benefits of treatment with SPORANOX® oral solution should therefore be weighed against the potential risk of breast-feeding. In case of doubt, the patient should not breast-feed.

Fertility
Refer to *Non-Clinical Information* for *in animal* fertility information relevant to itraconazole and hydroxypropyl-β-cyclodextrin.

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss (see *Adverse Reactions*), which may occur in some instances, must be taken into account.

Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of itraconazole based on the comprehensive assessment of the available adverse event information. A causal relationship with itraconazole usually cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trial data

The safety of SPORANOX® oral solution was evaluated in 889 patients who participated in six double-blind and four open-label clinical trials. Of the 889 patients treated with SPORANOX® oral solution, 624 patients were treated with SPORANOX® oral solution during the double-blind trials. All 889 patients received at least one dose of SPORANOX® oral solution for the treatment of oropharyngeal and esophageal candidiasis and provided safety data. Adverse reactions reported for ≥1% of patients treated with SPORANOX® oral solution in these clinical trials are shown in Table 1.

Table 1: Adverse Reactions Reported by ≥1% of Patients Treated with SPORANOX® Oral Solution in 10 Clinical Trials

System Organ Class Adverse Reaction	**SPORANOX® Oral Solution % (N=889)**
Nervous System Disorders	
Headache	3.6
Dysgeusia	1.5
Dizziness	1.1
Respiratory, Thoracic and Mediastinal Disorders	
Cough	1.8
Gastrointestinal Disorders	
Diarrhea	9.1
Nausea	8.2
Vomitings	5.2
Abdominal pain	4.5
Dyspepsia	1.0
Skin and Subcutaneous Tissue Disorders	
Rash	2.5
General Disorders and Administration Site Conditions	
Pyrexia	5.2

Adverse reactions that occurred in <1% of patients treated with SPORANOX® oral solution in these clinical trials are listed in Table 2.

Table 2: Adverse Reactions Reported by <1% of Patients Treated with SPORANOX® Oral Solution in 10 Clinical Trials

System Organ Class Adverse Reaction
Blood and Lymphatic System Disorders
Leukopenia
Thrombocytopenia
Immune System Disorders
Hypersensitivity

Table 2: Adverse Reactions Reported by <1% of Patients Treated with SPORANOX® Oral Solution in 10 Clinical Trials

Metabolism and Nutrition Disorders
Hypokalemia
Nervous System Disorders
Hypoesthesia
Neuropathy peripheral
Paresthesia
Ear and Labyrinth Disorders
Tinnitus
Cardiac Disorders
Cardiac failure
Gastrointestinal Disorders
Constipation
Hepatobiliary Disorders
Hepatic failure
Hyperbilirubinemia
Skin and Subcutaneous Tissue Disorders
Pruritus
Urticaria
Musculoskeletal and Connective Tissue Disorders
Arthralgia
Myalgia
Reproductive System and Breast Disorders
Menstrual disorder
General Disorders and Administration Site Conditions
Edema

The following is a list of additional adverse reactions associated with itraconazole that have been reported in clinical trials of SPORANOX® capsules and/or SPORANOX® IV, excluding the adverse reaction term "Injection site inflammation" which is specific to the injection route of administration.

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

Blood and Lymphatic System Disorders: Granulocytopenia

Immune System Disorders: Anaphylactoid reaction

Metabolism and Nutrition Disorders: Hyperglycemia, Hyperkalemia, Hypomagnesemia

Psychiatric Disorders: Confusional state

Nervous System Disorders: Somnolence

Cardiac Disorders: Left ventricular failure, Tachycardia

Vascular Disorders: Hypertension, Hypotension

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary edema, Dysphonia

Gastrointestinal Disorders: Gastrointestinal disorder, Flatulence

Hepatobiliary Disorders: Hepatitis, Jaundice, Hepatic function abnormal

Skin and Subcutaneous Tissue Disorders: Rash erythematous, Hyperhidrosis

Renal and Urinary Disorders: Renal impairment, Pollakiuria, Urinary incontinence

Reproductive System and Breast Disorders: Erectile dysfunction

General Disorders and Administration Site Conditions: Generalized edema, Face edema, Chest pain, Pain, Fatigue, Chills

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

Pediatrics

The safety of SPORANOX® oral solution was evaluated in 250 pediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least one dose of SPORANOX® oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data.

Based on pooled safety data from these clinical trials, the very common reported adverse reactions in pediatric patients were Vomiting (36.0%), Pyrexia (30.8%), Diarrhea (28.4%), Mucosal Inflammation (23.2%), Rash (22.8%), Abdominal pain (17.2%), Nausea (15.6%), Hypertension (14.0%), and Cough (11.2%). The nature of adverse reactions in pediatric patients is similar to that observed in adult subjects, but the incidence is higher in the pediatric patients.

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 3). The frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports.

In Table 3, adverse reactions are presented by frequency category based on incidence in clinical trials or epidemiology studies of SPORANOX® oral solution, when known.

Table 3: Adverse Reactions Identified During Post-Marketing Experience with SPORANOX® by Frequency Category Estimated from Clinical Trials or Epidemiologic Studies of SPORANOX® Oral Solution

Immune System Disorders	
Not known	Serum sickness, Angioneurotic edema, Anaphylactic reaction
Metabolism and Nutrition Disorders	
Not known	Hypertriglyceridemia
Nervous System Disorders	
Not known	Tremor
Eye Disorders	
Uncommon	Visual disturbances (including diplopia and vision blurred)
Ear and Labyrinth Disorders	
Not known	Transient or permanent hearing loss
Cardiac Disorders	
Not known	Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders	
Common	Dyspnea
Gastrointestinal Disorders	
Not known	Pancreatitis
Hepatobiliary Disorders	
Not known	Serious hepatotoxicity (including some cases of fatal acute liver failure)
Skin and Subcutaneous Tissue Disorders	
Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalized exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Investigations	
Not known	Blood creatine phosphokinase increased

Overdose

Symptoms and signs

In general, adverse events reported with overdose have been consistent with those reported for itraconazole use (see *Adverse Reactions*).

Treatment

In the event of an overdose, supportive measures should be employed.

It is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose.

Itraconazole cannot be removed by hemodialysis.

No specific antidote is available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

Mechanism of action

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.

Pharmacokinetic (PK) / Pharmacodynamic (PD) relationship

The PK/PD relationship for itraconazole, and for triazoles in general, is poorly understood.

Pharmacodynamic effects

Microbiology

Itraconazole, a triazole derivative, has a broad spectrum of activity.

For itraconazole, interpretive breakpoints have not been established by CLSI for the *Candida* spp. and filamentous fungi.

EUCAST breakpoints for itraconazole have been established for *Aspergillus flavus*, *A. fumigatus*, *A. nidulans* and *A. terreus*, and are as follows: susceptible ≤ 1 mg/L, resistant > 1 mg/L. EUCAST breakpoints for itraconazole have been established for *Candida albicans* and *C. dubliniensis*, and are as follows: susceptible ≤ 0.06 mg/L, resistant >0.06 mg/L. EUCAST breakpoints for itraconazole have been established for *Candida parapsilosis* and *C. tropicalis*, and are as follows: susceptible ≤ 0.125 mg/L, resistant >0.125 mg/L. Interpretive breakpoints have not been established by EUCAST for *Candida glabrata*, *C. krusei*, *C. guilliermondii*, *Cryptococcus neoformans*, *Aspergillus niger*, and Non-species related breakpoints for *Candida* and *Aspergillus*.

In vitro studies demonstrate that itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually ≤1 µg/ml. These include:

Aspergillus spp., *Blastomyces dermatitidis*, *Cladosporium* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Geotrichum* spp., *Histoplasma* spp., including *H. capsulatum*, *Paracoccidioides brasiliensis*, *Talaromyces (formerly Penicillium) marneffei*, *Sporothrix schenckii* and *Trichosporon* spp. Itraconazole also displayed activity *in vitro* against *Epidermophyton floccosum*, *Fonsecaea* spp., *Malassezia* spp., *Microsporum* spp., *Pseudallescheria boydii*, *Trichophyton* spp. and various other yeasts and fungi.

The principal fungus types that are not inhibited by itraconazole are Zygomycetes (e.g. *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14α-demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux. Cross-resistance between members of the azole class has been observed within *Candida* spp., although resistance to one member of the class does not necessarily confer resistance to other azoles. Itraconazole-resistant strains of *Aspergillus fumigatus* have been reported.

Pharmacokinetic Properties

Itraconazole

General pharmacokinetic characteristics

Peak plasma concentrations are reached within 2.5 hours following administration of the oral solution. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with C_{max} and AUC values 4 to 7-fold higher than those seen after a single dose. Steady-state C_{max} values of about 2 µg/ml are reached after oral administration of 200 mg once daily. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Absorption

Itraconazole is rapidly absorbed after administration of the oral solution. Peak plasma concentrations of itraconazole are reached within 2.5 hours following administration of the oral solution under fasting conditions. The observed absolute bioavailability of itraconazole under fed conditions is about 55% and increases by 30% when the oral solution is taken in fasting conditions.

Itraconazole exposure is greater with the oral solution than with the capsule formulation when the same dose of drug is given (see *Warnings and Precautions*).

Distribution

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

Metabolism
Itraconazole is extensively 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* antifungal activity comparable to itraconazole, trough plasma concentrations of this metabolite are about twice 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. Based on an oral radiolabeled dose, fecal excretion of unchanged drug ranges from 3% to 18% of the dose.

As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeks after discontinuation of a 4-week treatment and in nail keratin – where itraconazole can be detected as early as 1 week after start of treatment – for at least six months after the end of a 3-month treatment period.

Special populations

Hepatic impairment
Itraconazole is predominantly metabolized in the liver. A pharmacokinetic study was conducted in 6 healthy and 12 cirrhotic subjects who were administered a single 100-mg dose of itraconazole as a capsule. A statistically significant reduction in mean C_{max} (47%) and a twofold increase in the elimination half-life (37 ± 17 hours vs. 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC was similar in cirrhotic patients and in healthy subjects. Data are not available in cirrhotic patients during long-term use of itraconazole (see *Dosage and Administration* and *Warnings and Precautions*).

Renal impairment
Limited data are available on the use of oral itraconazole in patients with renal impairment. A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 ml/min. x 1.73 m^2, the bioavailability was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max}, C_{max}, and AUC_{0-8}). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50-79 ml/min), moderate (defined in this study as CrCl 20-49 ml/min), and severe renal impairment (defined in this study as CrCl <20 ml/min) were similar to that in healthy subjects, (range of means 42-49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively.) Overall exposure to itraconazole, based on AUC, was decreased in

patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole (see also *Dosage and Administration* and *Warnings and Precautions*).

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

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

NON-CLINICAL INFORMATION

Itraconazole
Itraconazole has been tested in a standard battery of non-clinical safety studies.

Acute oral toxicity studies with itraconazole in mice, rats, guinea pigs and dogs indicate a wide safety margin (4- to 16-fold of Maximum Recommended Human Dose [MRHD] of 400 mg/day based on mg/m^2/day). Sub (chronic) oral toxicity studies in rats and dogs revealed several target organs or tissues: adrenal cortex, liver and mononuclear phagocyte system as well as disorders of the lipid metabolism presenting as xanthoma cells in various organs.

At high doses of 40 and 80 mg/kg/day in rats (1- and 2-fold of MRHD based on mg/m^2/day), histological investigations of adrenal cortex showed a reversible swelling with cellular hypertrophy of the zona reticularis and fasciculata, which was sometimes associated with a thinning of the zona glomerulosa. Reversible hepatic changes were found at 40 and 160 mg/kg/day (1- and 4-fold of MRHD based on mg/m^2/day). Slight changes were observed in the sinusoidal cells and vacuolation of the hepatocytes, the latter indicating cellular dysfunction, but without visible hepatitis or hepatocellular necrosis. Histological changes of the mononuclear phagocyte system were mainly characterized by macrophages with increased proteinaceous material in various parenchymal tissues.

A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration. No toxicity was observed up to 20 mg/kg/day (2-fold of MRHD based on mg/m^2/day).

In three toxicology studies using rats, itraconazole induced bone defects. The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility.

Carcinogenicity and mutagenicity

Itraconazole is not a primary carcinogen in rats up to 13 mg/kg/day (males) and 52 mg/kg/day (females), or in mice up to 80 mg/kg/day (1-fold of MRHD based on mg/m^2/day). In male rats at 25 mg/kg/day dose (0.6-fold of MRHD based on mg/m^2/day), however, there was a higher incidence of soft-tissue sarcoma, which is attributed to the increase in non-neoplastic, chronic inflammatory reactions of the connective tissue as a consequence of raised cholesterol levels and cholesterosis in connective tissue.

There are no indications of a mutagenic potential of itraconazole.

Reproductive toxicology

Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at 40 and 160 mg/kg/day (1- and 4-fold of MRHD based on mg/m^2/day) and mice at 80 and 160 mg/kg/day (1- and 2-fold of MRHD based on mg/m^2/day). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and macroglossia. The observed skeletal malformation in rats may be due to maternal toxicity. No teratogenic effects were found in rabbits up to 80 mg/kg/day dose (4-fold of MRHD based on mg/m^2/day).

Fertility

There is no evidence of a primary influence on fertility under treatment with itraconazole.

Hydroxypropyl-β-cyclodextrin (HP-β-CD)

Single and repeated dose toxicity studies in mice, rats and dogs indicate a wide safety margin after oral and intravenous administration of HP-β-CD. Most effects were adaptive in nature (histological changes in the urinary tract, softening of feces related to the osmotic water retention in the large intestine, activation of the mononuclear phagocyte system) and showed good reversibility.

Slight liver changes occurred at doses of about 1.7 times the MRHD of HP-β-CD (16 g).

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.

Carcinogenicity and mutagenicity

No primary carcinogenicity activity was evidenced in the mouse carcinogenicity study. In the rat carcinogenicity study, an increased incidence of neoplasms in the large intestine (at 5000

mg/kg/day) and in the exocrine pancreas (from 500 mg/kg/day) were seen. Based on a human equivalent dose calculation normalized for body surface area, the maximum recommended clinical dose of SPORANOX® oral solution contains approximately 3.3 times the amount of HP-β-CD as was in the 500 mg/kg/day dose administered in rats in this carcinogenicity study.
The slightly higher incidence of adenocarcinomas in the large intestines was linked to the hypertrophic/hyperplastic and inflammatory changes in the colonic mucosa brought about by HP-β-CD-induced increased osmotic forces and is considered to be of low clinical relevance. Development of the pancreatic tumors is related to the mitogenic action of cholecystokinin in rats. This finding was not observed in the mouse carcinogenicity study, nor in a 12-month toxicity study in dogs or in a 2-year toxicity study in female cynomolgus monkeys. There is no evidence that cholecystokinin has a mitogenic action in man.

HP-β-CD is not mutagenic. 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.

Reproductive toxicology
HP-β-CD has no direct embryotoxic and no teratogenic effect, and is not mutagenic.

Fertility
HP-β-CD has no antifertile effect.

PHARMACEUTICAL INFORMATION

List of Excipients
Caramel, cherry flavor 1, cherry flavor 2, hydrochloric acid, hydroxypropyl-β-cyclodextrin, propylene glycol, purified water, sodium hydroxide, sodium saccharin and sorbitol.

Incompatibilities
None known.

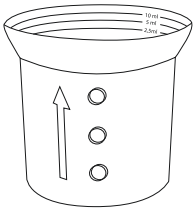
Shelf Life
See expiry date on the outer pack.
1 month after first opening the container.

Storage Conditions
Store at 25°C or below. Keep out of reach of children.

Nature and Contents of Container
150 ml amber glass bottle, with child-resistant polypropylene screw cap and LDPE liner ring.

Instructions for Use and Handling
SPORANOX® oral solution is supplied in bottles with a childproof cap, and should be opened as follows: push the plastic screw cap down while turning it counter clockwise.

A measuring cup is supplied with the SPORANOX® oral solution. Use the measuring cup just as it sits on the bottle. Make sure that the side with the graduations (the side that holds less) is uppermost; that is the side you have to fill. When the arrow on the side points up, the correct side is uppermost.



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DATE OF REVISION OF TEXT

15 June 2023 (CCDS 16 February 2023)