# PRODUCT NAME

## Trade name
SPORANOX® CAPSULES

## Generic Name/International Non-Proprietary Name
Itraconazole

# DOSAGE FORMS AND STRENGTHS
Each capsule, for oral administration, contains 100 mg itraconazole in a pellet formulation, and is available as a blue opaque cap and pink transparent body.

For excipients, see *List of Excipients.*

# CLINICAL INFORMATION

## Indications
SPORANOX® capsules are indicated for the following conditions:

- Gynecological indications:
  - Treatment of vulvovaginal candidosis.
- Dermatological / mucosal / ophthalmological indications:
  - Treatment of dermatomycosis, including highly keratinized regions as in plantar tinea pedis and palmar tinea manus;
  - Treatment of pityriasis versicolor;
  - Treatment of oral candidosis;
  - Treatment of fungal keratitis.
- Treatment of onychomycosis, caused by dermatophytes and/or yeasts.
- Systemic mycoses, only in the following fungal infections:
  - Treatment of systemic aspergillosis and candidosis;
  - Treatment of cryptococcosis (including cryptococcal meningitis): in immunocompromised patients with cryptococcosis and in patients with cryptococcosis of the central nervous system, only when first line treatment is considered inappropriate or has proven ineffective;
  - Histoplasmosis:
    - Treatment of histoplasmosis;
    - Maintenance therapy of histoplasmosis only in AIDS patients;
  - Treatment of blastomycosis;
  - Treatment of lymphocutaneous/cutaneous sporotrichosis;
  - Treatment of paracoccidioidomycosis;
  - Treatment of chromomycosis.

## Dosage and Administration
For optimal absorption, administer SPORANOX® capsules immediately after a full meal.

The capsules must be swallowed whole.

| Gynecological indication | | |
|---|---|---|
| **Indication** | **Dose** | **Treatment Duration** |
| Treatment of vulvovaginal candidosis | 200 mg twice daily<br>or<br>200 mg once daily | 1 day<br>or<br>3 days |

| Dermatological / mucosal / ophthalmological indications | | |
|---|---|---|
| **Indication** | **Dose** | **Treatment Duration** |
| Treatment of dermatomycosis | 200 mg once daily<br>or<br>100 mg once daily | 7 days<br>or<br>15 days |
| Treatment of dermatomycosis in highly keratinized regions as in plantar tinea pedis and palmar tinea manus | 200 mg twice daily<br>or<br>100 mg once daily | 7 days<br>or<br>30 days |
| Treatment of pityriasis versicolor | 200 mg once daily | 7 days |
| Treatment of oral candidosis | 100 mg once daily | 15 days |
| Treatment of fungal keratitis | 200 mg once daily | 21 days<br>The duration of treatment should be adjusted to the clinical response. |

| Onychomycosis, caused by dermatophytes and/or yeasts | |
|---|---|
| Onychomycosis<br>**Pulse treatment** | Dose and Treatment duration |
| | A pulse treatment consists of two capsules twice daily (200 mg twice daily) for one week. Two pulse treatments are recommended for fingernail infections, and three pulse treatments for toenail infections. Pulse treatments are always separated by a 3-week drug-free interval. Clinical response will become evident as the nail re-grows, following discontinuation of the treatment. |

| Site of onychomycosis | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 |
|---|---|---|---|---|---|---|---|---|---|
| Toenails with or without fingernail involvement | Pulse 1 | Itraconazole-free weeks | | | Pulse 2 | Itraconazole-free weeks | | | Pulse 3 |
| Fingernails only | Pulse 1 | Itraconazole-free weeks | | | Pulse 2 | | | | |

| Onychomycosis<br>**Continuous treatment** | Dose | Treatment duration |
|---|---|---|
| Toenails with or without fingernail involvement | 200 mg once daily | 3 months |

Elimination of itraconazole from skin and nail tissue is slower than from plasma. Optimal clinical and mycological response is thus reached 2 to 4 weeks after the cessation of treatment for skin infections and 6 to 9 months after the cessation of treatment for nail infections.

| **Systemic mycoses** | | | |
|---|---|---|---|
| **Indication** | **Dose** | **Median Treatment Duration[1]** | **Remarks** |
| Treatment of aspergillosis | 200 mg once daily | 2-5 months | Increase dose to 200 mg twice daily in case of invasive or disseminated disease. |
| Treatment of candidosis | 100 - 200 mg once daily | 3 weeks - 7 months | Increase dose to 200 mg twice daily in case of invasive or disseminated disease. |
| Treatment of non-meningeal cryptococcosis | 200 mg once daily | 2 months - 1 year | |
| Treatment of cryptococcal meningitis | 200 mg twice daily | 2 months -1 year | |
| Treatment of histoplasmosis | 200 mg once daily - 200 mg twice daily | 8 months | |
| Histoplasmosis (maintenance therapy only in AIDS patients) | 200mg once or twice daily | *Until immune recovery*[2] | |
| Treatment of blastomycosis | 100 mg once daily - 200 mg twice daily | 6 months | |
| Treatment of lymphocutaneous and cutaneous sporotrichosis | 100 mg or 200mg once daily | 3 months to 6 months | |
| Treatment of paracoccidioidomycosis | 100 mg once daily | 6 months | Data on the efficacy of SPORANOX® capsules at this dosage for treatment of paracoccidioidomycosis in patients with AIDS is not available. |
| Treatment of chromomycosis | 200 mg once daily | 6 months | |
| [1] The duration of treatment should be adjusted depending on the clinical response.<br>[2]The duration of treatment should be based upon the status of immune recovery. | | | |

## Special populations

### *Pediatrics*

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

### *Elderly*
Clinical data on the use of SPORANOX® capsules in elderly patients are limited. It is advised to use SPORANOX® capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be 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® capsules are 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® capsules. Increased plasma concentrations of these drugs, caused by coadministration with itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that 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® capsules should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see *Warnings and Precautions).* SPORANOX® capsules must not be used during pregnancy (except for life-threatening cases) (see *Pregnancy, Breast-feeding and Fertility).*

Women of childbearing potential taking SPORANOX® should use contraceptive precautions. Highly effective contraception should be continued until the menstrual period following the end of SPORANOX® 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® capsules to patients with hypersensitivity to other azoles.

### Neuropathy

If neuropathy occurs that may be attributable to SPORANOX® capsules, 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 pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking other hepatotoxic drugs. Some patients had no obvious risk factors for liver disease. Some of these cases were observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving 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 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*)

## Reduced gastric acidity

Absorption of itraconazole from SPORANOX® capsules is impaired when gastric acidity is reduced. In patients with reduced gastric acidity, whether from disease (e.g. patients with achlorhydria) or from concomitant medication (e.g. patients taking drugs that reduce gastric acidity), it is advisable to administer SPORANOX® capsules with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary (see *Interactions* and *Pharmacokinetic Properties - Absorption*).

## Pediatrics

Clinical data on the use of SPORANOX® capsules in pediatric patients are limited. The use of SPORANOX® capsules 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® capsules in elderly patients are limited. It is advised to use SPORANOX® capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be 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*).

### Immunocompromised patients
In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), the oral bioavailability of SPORANOX® capsules may be decreased. Therefore, the dose should be adjusted based on the clinical response in these patients.

### Patients with immediately life-threatening systemic fungal infections
Due to the pharmacokinetic properties (see *Pharmacokinetics Properties*), SPORANOX® capsules are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

### Patients with AIDS
In patients with AIDS who have received treatment for a systemic fungal infection with SPORANOX® capsules and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

### 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 bid. Steady state concentrations of >250ng/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® capsules, consideration should be given to switching to alternative therapy.

## 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. Absorption of itraconazole from the capsule formulation is reduced in subjects with reduced gastric acidity. Drugs that reduce gastric acidity impair the absorption of itraconazole from itraconazole capsules. To counteract this effect, it is recommended to administer itraconazole capsules with an acidic beverage (such as non-diet cola) upon coadministration with drugs that reduce gastric acidity. (see *Warnings and Precautions*)

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:
    - Drugs that reduce gastric acidity (itraconazole capsules only)
    - 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 above for additional info) |
|---|---|---|
| **Alpha Blockers** | | |
| Alfuzosin<br>Silodosin<br>Tamsulosin | Alfuzosin $C_{max}$ (↑↑), AUC (↑↑)[a]<br>Silodosin $C_{max}$ (↑↑), AUC (↑↑)[a]<br>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<br>Buprenorphine (IV and sublingual)<br>Oxycodone<br>Sufentanil | Alfentanil AUC (↑↑ to ↑↑↑↑)[a]<br>Buprenorphine $C_{max}$ (↑↑), AUC (↑↑)[a]<br><br>Oxycodone $C_{max}$ ↑, AUC ↑↑<br>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]<br>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. |
| **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. |

| Examples of medicinal products within class | Expected/Potential effect on drug levels (see footnotes for additional info) | Clinical comment (see above for additional info) |
|---|---|---|
| **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<br>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]<br>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<br><br>Trimetrexate | Delamanid conc. increase (extent unknown)[a,b]<br>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<br>Rifampicin | Isoniazid: itraconazole conc. (↓↓↓)[a,b]<br>Rifampicin: itraconazole AUC ↓↓↓ | Not recommended from 2 weeks before and during treatment with itraconazole,<br>Itraconazole efficacy may be reduced. |
| Rifabutin | Rifabutin conc. increase (extent unknown)[a,b]<br>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]. |
| Telithromycin | In healthy subjects: telithromycin $C_{max}$ ↑, AUC ↑<br>In severe renal impairment: telithromycin AUC (↑↑)[a]<br>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[c], such as hepatotoxicity, QT prolongation and TdPs.<br>Use with caution in other patients:, monitor for telithromycin adverse reactions, dose reduction of telithromycin may be necessary. |
| **Anticoagulants and Antiplatelet Drugs** | | |
| Apixaban<br>Edoxaban<br>Rivaroxaban<br>Vorapaxar | Apixaban $C_{max}$ (↑), AUC (↑)[a]<br>Edoxaban $C_{max}$ (↑), AUC (↑)[a]<br>Rivaroxaban $C_{max}$ (↑), AUC (↑ to ↑↑)[a]<br>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 (eg, warfarin)<br>Cilostazol | Coumarins (eg, warfarin) conc increase (extent unknown)[a,b]<br>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 |

| Examples of medicinal products within class | Expected/Potential effect on drug levels (see footnotes for additional info) | Clinical comment (see above for additional info) |
|---|---|---|
| | | ticagrelor-related adverse reactions, such as bleeding. |
| **Anticonvulsants** | | |
| Carbamazepine | Carbamazepine conc. (↑)[a,b]<br>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<br>Phenytoin | Phenobarbital: itraconazole conc. (↓↓↓)[a,b]<br>Phenytoin: itraconazole AUC ↓↓↓ | Not recommended from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced. |
| **Antidiabetics** | | |
| Repaglinide<br>Saxagliptin | Repaglinide $C_{max}$ ↑, AUC ↑<br>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<br>Quinine | Artemether $C_{max}$ (↑↑), AUC (↑↑)[a]<br>Lumefantrine $C_{max}$ (↑), AUC (↑)[a]<br>Quinine $C_{max}$ ↔, AUC ↑ | Use with caution, monitor for artemether-lumefantrine/quinine adverse reactions[c]. Refer to the label for specific actions to be taken. |
| 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<br>Ebastine<br>Rupatadine | Bilastine $C_{max}$ (↑↑), AUC (↑)[a]<br>Ebastine $C_{max}$ ↑↑, AUC ↑↑↑<br>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. |

| **Examples of medicinal products within class** | **Expected/Potential effect on drug levels (see footnotes for additional info)** | **Clinical comment (see above for additional info)** |
|---|---|---|
| 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<br>Brentuximab vedotin<br>Busulfan<br>Erlotinib<br>Gefitinib<br>Imatinib<br>Ixabepilone<br>Nintedanib<br>Panobinostat<br>Pemigatinib<br>Ponatinib<br>Ruxolitinib<br>Sonidegib<br>Tretinoin (oral)<br>Vandetanib | Bortezomib AUC (↑)[a]<br>Brentuximab vedotin AUC (↑)[a]<br>Busulfan $C_{max}$ ↑, AUC ↑<br>Erlotinib $C_{max}$ (↑↑), AUC (↑)[a]<br>Gefitinib $C_{max}$ ↑, AUC ↑<br>Imatinib $C_{max}$ (↑), AUC (↑)[a]<br>Ixabepilone $C_{max}$ (↔), AUC (↑)[a]<br>Nintedanib $C_{max}$ (↑), AUC (↑)[a]<br>Panobinostat $C_{max}$ (↑), AUC (↑)[a]<br>Pemigatinib $C_{max}$ ↑, AUC ↑<br>Ponatinib $C_{max}$ (↑), AUC (↑)[a]<br>Ruxolitinib $C_{max}$ (↑), AUC (↑)[a]<br>Sonidegib $C_{max}$ (↑), AUC (↑↑)[a]<br>Tretinoin $C_{max}$ (↑), AUC (↑)[a]<br>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]<br>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<br>Bosutinib<br>Cabazitaxel<br>Cabozantinib<br>Ceritinib<br>Cobimetinib<br>Crizotinib<br>Dabrafenib<br>Dasatinib<br>Docetaxel<br>Entrectinib<br>Glasdegib<br>Ibrutinib | Axitinib $C_{max}$ (↑), AUC (↑↑)[a]<br>Bosutinib $C_{max}$ (↑↑↑), AUC (↑↑↑)[a]<br>Cabazitaxel $C_{max}$ (↔), AUC (↔)[a]<br>Cabozantinib $C_{max}$ (↔), AUC (↑)[a]<br>Ceritinib $C_{max}$ (↑), AUC (↑↑)[a]<br>Cobimetinib $C_{max}$ ↑↑, AUC ↑↑↑<br>Crizotinib $C_{max}$ (↑), AUC (↑↑)[a]<br>Dabrafenib AUC (↑)[a]<br>Dasatinib $C_{max}$ (↑↑), AUC (↑↑)[a]<br>Docetaxel AUC (↔ to ↑↑)[a]<br>Entrectinib $C_{max}$ ↑, AUC ↑↑↑<br>Glasdegib $C_{max}$ (↑), AUC (↑↑)[a]<br>Ibrutinib $C_{max}$ (↑↑↑↑), AUC (↑↑↑↑)[a] | Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the antineoplastic drug[c].<br>Additionally:<br>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.<br>For ibrutinib, 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 above for additional info)** |
|---|---|---|
| Lapatinib<br>Nilotinib<br>Olaparib<br>Pazopanib<br>Sunitinib<br>Talazoparib<br>Trabectedin<br>Trastuzumab emtansine<br><br>Vinca alkaloids | Lapatinib $C_{max}$ (↑↑), AUC (↑↑)[a]<br>Nilotinib $C_{max}$ (↑), AUC (↑↑)[a]<br>Olaparib $C_{max}$ ↑, AUC ↑↑<br>Pazopanib $C_{max}$ (↑), AUC (↑)[a]<br>Sunitinib $C_{max}$ (↑), AUC (↑)[a]<br>Talazoparib $C_{max}$ ↑, AUC ↑<br>Trabectedin $C_{max}$ (↑), AUC (↑)[a]<br>Trastuzumab emtansine conc increase (extent unknown)[a,b]<br><br>Vinca alkaloid conc increase (extent unknown)[a,b] | |
| 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. |
| 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<br>Aripiprazole<br>Brotizolam<br>Buspirone<br>Cariprazine<br>Haloperidol<br>Midazolam (iv)<br>Perospirone<br>Quetiapine<br>Ramelteon<br>Risperidone<br>Suvorexant<br>Zopiclone | Alprazolam $C_{max}$ ↔, AUC ↑↑<br>Aripiprazole $C_{max}$ ↑, AUC ↑<br>Brotizolam $C_{max}$ ↔, AUC ↑↑<br>Buspirone $C_{max}$ ↑↑↑↑, AUC ↑↑↑↑<br>Cariprazine (↑↑)[a,b]<br>Haloperidol $C_{max}$ ↑, AUC ↑<br>Midazolam (iv) conc increase ↑↑[b]<br>Perospirone $C_{max}$ ↑↑↑, AUC ↑↑↑<br>Quetiapine $C_{max}$ (↑↑), AUC (↑↑↑)[a]<br>Ramelteon $C_{max}$ (↑), AUC (↑)[a]<br>Risperidone conc increase ↑[b]<br>Suvorexant $C_{max}$ (↑), AUC (↑↑)[a]<br>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 |

| **Examples of medicinal products within class** | **Expected/Potential effect on drug levels (see footnotes for additional info)** | **Clinical comment (see above for additional info)** |
|---|---|---|
| | | 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 as seizures, respiratory depression, angioedema, apnea and coma. |
| **Antivirals** | | |
| Asunaprevir<br>Tenofovir disoproxil fumarate (TDF) | Asunaprevir $C_{max}$ (↑↑↑), AUC (↑↑↑)[a]<br>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]<br>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]<br>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<br>Vaniprevir | Daclatasvir $C_{max}$ (↑), AUC (↑↑)[a]<br>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)<br>Fosamprenavir (ritonavir-boosted) | Ritonavir-boosted darunavir: itraconazole $C_{max}$ (↑↑), AUC (↑↑)[a]<br>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]<br>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; |

| Examples of medicinal products within class | Expected/Potential effect on drug levels (see footnotes for additional info) | Clinical comment (see above for additional info) |
|---|---|---|
| | | refer to the elvitegravir label for specific actions to be taken. |
| Efavirenz<br>Nevirapine | Efavirenz: itraconazole $C_{max}$ ↓, AUC ↓<br>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]<br>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]<br>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]<br>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. |
| Ombitasvir/ Paritaprevir/Ritonavir with or without Dasabuvir | Itraconazole $C_{max}$ (↑), AUC (↑↑)[a]<br>Ombitasvir $C_{max}$ (↔), AUC (↑)[a]<br>Paritaprevir $C_{max}$ (↑), AUC (↑↑)[a]<br>Ritonavir $C_{max}$ (↑), AUC (↑)[a]<br>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]<br>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 ↑↑↑<br>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. |

| **Examples of medicinal products within class** | **Expected/Potential effect on drug levels (see footnotes for additional info)** | **Clinical comment (see above for additional info)** |
|---|---|---|
| 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<br>Lercanidipine<br>Nisoldipine | Felodipine $C_{max}$ ↑↑↑, AUC ↑↑↑<br>Lercanidipine AUC (↑↑↑↑)[a]<br>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<br><br>Verapamil | Dihydropyridine conc increase (extent unknown)[a,b]<br>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<br>Riociguat<br>Sildenafil (pulmonary hypertension)<br>Tadalafil (pulmonary hypertension) | Aliskiren $C_{max}$ ↑↑↑, AUC ↑↑↑<br>Riociguat $C_{max}$ (↑), AUC (↑↑)[a]<br>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. |
| Bosentan<br>Guanfacine | Bosentan $C_{max}$ (↑↑), AUC (↑↑)[a]<br>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<br>Ulipristal | Dienogest $C_{max}$ (↑), AUC (↑↑)[a]<br>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<br>Loperamide | Aprepitant AUC (↑↑↑)[a]<br>Loperamide $C_{max}$ ↑↑, AUC ↑↑ | Use with caution, monitor for aprepitant/loperamide/netupitant adverse |

| **Examples of medicinal products within class** | **Expected/Potential effect on drug levels (see footnotes for additional info)** | **Clinical comment (see above for additional info)** |
|---|---|---|
| Netupitant | Netupitant $C_{max}$ (↑), AUC (↑↑)[a] | 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. |
| Drugs that reduce gastric acidity | Itraconazole: $C_{max}$ ↓↓, AUC ↓↓ | Use with caution: Drugs that reduce gastric acidity: e.g. acid neutralizing medicines such as aluminum hydroxide, or acid secretion suppressors such as H2- receptor antagonists and proton pump inhibitors.<br>When co-treatment with acid neutralizing medicines (e.g. aluminum hydroxide) these should be administered at least 2 hours before or 2 hours after the intake of SPORANOX® capsules. (See *Warnings and Precautions*.) |
| 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)[a,b] | Not recommended during and for 2 weeks after treatment with itraconazole. S. boulardii efficacy may be reduced. |
| **Immunosuppressants** | | |
| Budesonide<br><br><br>Ciclesonide<br><br>Cyclosporine<br><br><br><br>Dexamethasone<br><br><br>Fluticasone | Budesonide (inhalation) $C_{max}$ ↑, AUC ↑↑; Budesonide (other form.) conc increase (extent unknown)[a,b]<br>Ciclesonide (inhalation) $C_{max}$ (↑↑), AUC (↑↑)[a]<br>Cyclosporine (iv) conc increase ↔ to ↑[b]<br>Cyclosporine (other form.) conc increase (extent unknown)[a,b]<br>Dexamethasone $C_{max}$ ↔ (iv) ↑ (oral), AUC ↑↑ (iv, oral)<br>Fluticasone (inhalation) conc increase ↑↑[b]<br>Fluticasone (nasal) conc increase (↑)[a,b] | Use with caution, monitor for immunosuppressant adverse reactions[c], Dose reduction of the immunosuppressant drug may be necessary. |

| **Examples of medicinal products within class** | **Expected/Potential effect on drug levels (see footnotes for additional info)** | **Clinical comment (see above for additional info)** |
|---|---|---|
| Methylprednisolone<br><br><br>Tacrolimus<br><br>Temsirolimus | Methylprednisolone (oral) $C_{max}$ ↑ to ↑↑, AUC ↑↑<br>Methylprednisolone (iv) AUC ↑↑<br>Tacrolimus (iv) conc increase ↑[b]<br>Tacrolimus (oral) $C_{max}$ (↑↑), AUC (↑↑)[a]<br>Temsirolimus (iv) $C_{max}$ (↑↑), AUC (↑↑)[a] | |
| Everolimus<br>Sirolimus (rapamycin) | Everolimus $C_{max}$ (↑↑), AUC (↑↑↑↑)[a]<br>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<br>Simvastatin | Lovastatin $C_{max}$ ↑↑↑↑, AUC ↑↑↑↑<br>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. |
| **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<br>Venlafaxine | Reboxetine $C_{max}$ (↔), AUC (↑)[a]<br>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. |

| **Examples of medicinal products within class** | **Expected/Potential effect on drug levels (see footnotes for additional info)** | **Clinical comment (see above for additional info)** |
|---|---|---|
| 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<br><br>Vardenafil | Darifenacin $C_{max}$ (↑↑↑), AUC (↑↑↑ to ↑↑↑↑)[a]<br>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<br><br>Imidafenacin<br>Oxybutynin<br>Sildenafil (erectile dysfunction)<br>Tadalafil (erectile dysfunction and benign prostatic hyperplasia)<br>Tolterodine<br><br>Udenafil | Dutasteride conc increase (extent unknown)[a,b]<br>Imidafenacin $C_{max}$ ↑, AUC ↑<br>Oxybutynin conc increase ↑[b]<br>Sildenafil $C_{max}$ (↑↑), AUC (↑↑ to ↑↑↑↑)[a]<br>Tadalafil $C_{max}$ (↑), AUC (↑↑)[a]<br><br><br>Tolterodine $C_{max}$ (↑ to ↑↑), AUC (↑↑)[a] in poor metabolizers of CYP2D6<br>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.<br>(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.<br>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.<br>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)<br>Cabergoline<br>Cannabinoids<br><br>Cinacalcet | Alitretinoin $C_{max}$ (↑), AUC (↑)[a]<br>Cabergoline $C_{max}$ (↑↑), AUC (↑↑)[a]<br>Cannabinoids conc increase, extent unknown but likely (↑↑)[a]<br>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 Cmax (↑), AUC (↑↑)[a] | Use with caution, monitor for valbenazine-related adverse reactions[c], dose reduction of valbenazine is necessary. |

| **Examples of medicinal products within class** | **Expected/Potential effect on drug levels (see footnotes for additional info)** | **Clinical comment (see above for additional info)** |
|---|---|---|
| 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.<br>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]<br>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.<br>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.<br>(see also *Antimigraine Drugs*) |
| 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]<br>Lumacaftor $C_{max}$ (↔), AUC (↔)[a]<br>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<br>Tolvaptan | Conivaptan $C_{max}$ (↑↑), AUC (↑↑↑↑)[a]<br>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. |

| Examples of medicinal products within class | Expected/Potential effect on drug levels (see footnotes for additional info) | Clinical comment (see above for additional info) |
|---|---|---|

*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® capsules 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 SPORANOX® capsules therapy 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.

## 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® capsules was evaluated in 8499 patients who participated in 107 open-label and double-blind clinical trials. Of the 8499 patients treated with SPORANOX® capsules, 2104 patients were treated with SPORANOX® capsules during double-blind trials. All 8499 patients received at least one dose of SPORANOX® capsules for the treatment of dermatomycoses or onychomycosis and provided safety data. Adverse reactions reported for ≥1% of patients treated with SPORANOX® capsules in these clinical trials are shown in Table 1.

**Table 1: Adverse Reactions Reported by ≥1% of Patients Treated with SPORANOX® in 107 Clinical Trials**

| **System Organ Class**<br>Adverse Reaction | **SPORANOX® Capsules %<br>(N=8499)** |
|---|---|
| **Nervous System Disorders** | |
| Headache | 1.6 |
| **Gastrointestinal Disorders** | |
| Nausea | 1.6 |

**Table 1: Adverse Reactions Reported by ≥1% of Patients Treated with SPORANOX® in 107 Clinical Trials**

| **System Organ Class**<br>Adverse Reaction | **SPORANOX® Capsules %**<br>**(N=8499)** |
|---|---|
| Abdominal pain | 1.3 |

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

**Table 2: Adverse Reactions Reported by <1% of Patients Treated with SPORANOX® Capsules in 107 Clinical Trials**

| **System Organ Class**<br>Adverse Reaction |
|---|
| **Infections and Infestations** |
| Rhinitis |
| Sinusitis |
| Upper respiratory tract infection |
| **Blood and Lymphatic System Disorders** |
| Leukopenia |
| **Immune System Disorders** |
| Hypersensitivity |
| **Nervous System Disorders** |
| Dysgeusia |
| Hypoesthesia |
| Paresthesia |
| **Ear and Labyrinth Disorders** |
| Tinnitus |
| **Gastrointestinal Disorders** |
| Constipation |
| Diarrhea |
| Dyspepsia |
| Flatulence |
| Vomiting |
| **Hepatobiliary Disorders** |
| Hepatic function abnormal |
| Hyperbilirubinemia |
| **Skin and Subcutaneous Tissue Disorders** |
| Pruritus |
| Rash |
| Urticaria |
| **Renal and Urinary Disorders** |
| Pollakiuria |
| **Reproductive System and Breast Disorders** |
| Erectile dysfunction |
| 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® oral solution and/or SPORANOX® IV, excluding the adverse reaction term "Injection site inflammation" which is specific to the injection route of administration.

**Blood and Lymphatic System Disorders:** Granulocytopenia, Thrombocytopenia

**Immune System Disorders:** Anaphylactoid reaction

**Metabolism and Nutrition Disorders:** Hyperglycemia, Hyperkalemia, Hypokalemia, Hypomagnesemia

**Psychiatric Disorders:** Confusional state

**Nervous System Disorders:** Neuropathy peripheral, Dizziness, Somnolence, Tremor

**Cardiac Disorders:** Cardiac failure, Left ventricular failure, Tachycardia

**Vascular Disorders:** Hypertension, Hypotension

**Respiratory, Thoracic and Mediastinal Disorders:** Pulmonary edema, Dysphonia, Cough

**Gastrointestinal Disorders:** Gastrointestinal disorder

**Hepatobiliary Disorders:** Hepatic failure, Hepatitis, Jaundice

**Skin and Subcutaneous Tissue Disorders:** Rash erythematous, Hyperhidrosis

**Musculoskeletal and Connective Tissue Disorders:** Myalgia, Arthralgia

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

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

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

### *Pediatrics*

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

Based on pooled safety data from these clinical trials, the commonly reported adverse reactions in pediatric patients were Headache (3.0%), Vomiting (3.0%), Abdominal pain (2.4%), Diarrhea (2.4%), Hepatic function abnormal (1.2%), Hypotension (1.2%), Nausea (1.2%), and Urticaria (1.2%). In general, 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.

### Post-marketing 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® capsules, 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® Capsules**

| | |
|---|---|
| **Immune System Disorders** | |
| *Not known* | Serum sickness, Angioneurotic edema, Anaphylactic reaction |
| **Metabolism and Nutrition Disorders** | |
| *Not known* | Hypertriglyceridemia |
| **Nervous System Disorders** | |
| *Rare* | Tremor |
| **Eye Disorders** | |
| *Rare* | 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** | |
| *Rare* | Dyspnea |
| **Gastrointestinal Disorders** | |
| *Rare* | Pancreatitis |
| **Hepatobiliary Disorders** | |
| *Not known* | Serious hepatotoxicity (including some cases of fatal acute liver failure) |
| **Skin and Subcutaneous Tissue Disorders** | |
| *Rare* | Alopecia |
| *Not known* | Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalized exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, 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 *Candida* spp. and the 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, Crytococcus neoformans, Geotrichum* spp., including *H. capsulatum, Paracoccidioides brasiliensis, Talaromyces* (formerly *Penicillium) marneffei, Sporothrix schenckii* and *Trichosporon* spp. Itraconazole also displayed activity *in vitro* against *Epidermophyton floccosum, Fonsecacea* 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

### General pharmacokinetic characteristics

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. 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 $C_{max}$ values of 0.5 µg/mL, 1.1 µg/mL and 2.0 µg/mL after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single 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 oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral capsule dose. The observed absolute oral bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., $H_2$-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see *Warnings and Precautions*, and *Interactions*). Absorption of itraconazole under fasted conditions in these subjects is increased when SPORANOX® capsules are administered with an acidic beverage (such as a non-diet cola). When SPORANOX® capsules were administered as a single 200-mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a $H_2$-receptor

antagonist, itraconazole absorption was comparable to that observed when SPORANOX® capsules were administered alone (see *Interactions*).

Itraconazole exposure is lower with the capsule formulation than with the oral solution 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 (> 700L), suggesting extensive distribution into tissues. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma, and the uptake into keratinous tissues, skin in particular, up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

### Metabolism

Itraconazole is extensively 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.

## NON-CLINICAL INFORMATION

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 an 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.

# PHARMACEUTICAL INFORMATION

## List of Excipients

The inactive ingredients of the capsules are hypromellose, macrogol, and sugar spheres (composed of maize starch, purified water, and sucrose), alcohol and methylene chloride.

The capsule itself contains erythrosine sodium, gelatin, indigotin disulfonate sodium, titanium dioxide.

## Incompatibilities
None known.

## Shelf life
See expiry date on the outer pack.

## Storage Conditions
Store between 15°C and 30°C. Keep out of the sight and reach of children.

## Nature and Contents of Container
SPORANOX® is available as blue opaque cap and pink transparent body, containing 100 mg of itraconazole in a pellet formulation, supplied in blister packs with 4, 6, 15, 28 or 60 capsules. Not all presentations may be available locally.

## PRODUCT REGISTRANT
Johnson & Johnson International (Singapore) Pte. Ltd.
2, Science Park Drive
#07-13, Ascent
Singapore Science Park 1
Singapore 118222

## BATCH RELEASER
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