Sporanox™ (itraconazole)
Capsules

NAME OF MEDICINAL PRODUCT
Sporanox Capsules

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 100 mg itraconazole in a pellet formulation.

PHARMACEUTICAL FORM
Capsules for oral administration.

CLINICAL PARTICULARS
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;
- Prophylaxis of fungal infections in immunocompromised patients with severe neutropenia.
- Cryptococcosis (including cryptococcal meningitis):
– Treatment of immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system, only when first line treatment is considered inappropriate or has proven ineffective;
– For maintenance therapy of cryptococcal meningitis in AIDS patients, only when first line treatment is considered inappropriate or has proven ineffective.
- Treatment of histoplasmosis;
- Histoplasmosis, maintenance therapy only in AIDS patients;
- Penicilliosis, maintenance therapy only in AIDS patients;
- Treatment of blastomycosis;
- Treatment of sporotrichosis, including lymphocutaneous/cutaneous and extracutaneous;
- 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 or 200 mg once daily	1 day or 3 days

Dermatological / mucosal / ophthalmological indications		
Indication	**Dose**	**Treatment Duration**
Treatment of dermatomycosis	200 mg once daily or 100 mg once daily	7 days or 15 days
Treatment of dermatomycosis in highly keratinized regions as in plantar tinea pedis and palmar tinea manus	200 mg twice daily or 100 mg once daily	7 days or 30 days
Treatment of pityriasis versicolor	100 mg twice daily or 200 mg once daily	5 - 7 days
Treatment of oral candidosis	100 mg once daily	15 days
Treatment of fungal keratitis	200 mg once daily	21 days The duration of treatment should be adjusted to the clinical response.

Onychomycosis, caused by dermatophytes and/or yeasts	
Onychomycosis **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 **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.
Prophylaxis of fungal infections in immunocompromised patients with severe neutropenia	200 mg twice daily	*Until immune recovery*[2]	Initiate 1-3 days prior to or at start of chemotherapy until neutropenia resolves.
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	
Cryptococcal meningitis (maintenance therapy only in AIDS patients)	200 mg once daily	*Until immune recovery*[2]	
Treatment of histoplasmosis	200 mg once daily - 200 mg twice daily	8 months	
Histoplasmosis (maintenance therapy only in AIDS patients)	200 mg once or twice daily	*Until immune recovery*[2]	
Penicilliosis (maintenance therapy only in AIDS patients)	200 mg 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 200 mg once daily (localized lesions) or 200 mg twice daily (extensive lesions)	3 months to 6 months	
Treatment of extracutaneous sporotrichosis	200 mg twice daily	12 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.
[2] The duration of treatment should be based upon the status of the 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.
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.
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.
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.

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. (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, Lactation 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 CHF. 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 CHF or with a history of CHF 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 CHF. 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 CHF, 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. 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. 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.
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.
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 *Pharmacokinetics 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.
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, 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 > 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 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. This list of examples 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.

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:
o 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:
o Moderate or potent CYP3A4 inducers: not recommended from 2 weeks before and during treatment with itraconazole
o 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:
o Drugs that reduce gastric acidity (itraconazole capsules only)
o Moderate or potent inhibitors of CYP3A4
o CYP3A4/P-gp/BCRP substrates for which increased or decreased plasma concentrations result in a clinically relevant risk
Examples of interacting drugs are listed in the table below. The drugs listed in this table are based on either drug interaction studies or case reports, or potential interactions based on the mechanism of interaction.

Medicinal products within class	**Clinical comment**
Alpha Blockers	
Alfuzosin Silodosin Tamsulosin	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of alfuzosin/silodosin/tamsulosin-related adverse reactions
Analgesics	
Alfentanil Buprenorphine Oxycodone Sufentanil	Use with caution, monitor for adverse reactions related to the analgesic, dose reduction of alfentanil/buprenorphine/oxycodone/ sufentanil may be necessary.
Fentanyl	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of fentanyl-related adverse reactions
Levacetylmethadol	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of levacetylmethadol-related adverse reactions, such as QT prolongation and TdP.
Methadone	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	Use with caution, monitor for digoxin adverse reactions, dose reduction of digoxin may be necessary.
Disopyramide	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of disopyramide-related adverse reactions, such as serious arrhythmias including TdP.
Dofetilide	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	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	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	Not recommended, coadministration for more than 2 weeks at any time during bedaquiline dosing is not recommended: increased risk of bedaquiline-related adverse reactions.
Ciprofloxacin Erythromycin	Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
Clarithromycin	Use with caution, monitor for adverse reactions related to itraconazole and/or clarithromycin, dose reduction of itraconazole and/or clarithromycin may be necessary.
Delamanid Trimetrexate	Use with caution, monitor for delamanid/trimetrexate adverse reactions, dose reduction of delamanid/trimetrexate may be necessary
Isoniazid Rifampicin	Not recommended from 2 weeks before and during treatment with itraconazole, Itraconazole efficacy may be reduced.
Rifabutin	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
Telithromycin	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. Use with caution in other patients:, monitor for telithromycin adverse reactions, dose reduction of telithromycin may be necessary
Anticoagulants and Antiplatelet Drugs	
Apixaban Rivaroxaban Vorapaxar	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of apixaban/rivaroxaban/vorapaxar-related adverse reactions
Coumarins Cilostazol	Use with caution, monitor for coumarins/cilostazol adverse reactions, dose reduction of coumarins/cilostazol may be necessary
Dabigatran	Use with caution, monitor for dabigatran adverse reactions, dose reduction of dabigatran may be necessary
Ticagrelor	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ticagrelor-related adverse reactions, such as bleeding
Anticonvulsants	
Carbamazepine	Not recommended from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of carbamazepine related adverse reactions.
Phenobarbital Phenytoin	Not recommended from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of carbamazepine related adverse reactions
Antidiabetics	
Repaglinide Saxagliptin	Use with caution, monitor for repaglinide/saxagliptin adverse reactions, dose reduction of repaglinide/saxagliptin may be necessary
Antihelminthics, antifungals and antiprotozoals	
Artemether-lumefantrine Quinine	Use with caution, monitor for artemether-lumefantrine/quinine adverse reactions
Halofantrine	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	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	Use with caution, monitor for praziquantel adverse reactions, dose reduction of praziquantel may be necessary
Antihistamines	
Astemizole	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	Use with caution, monitor for bilastine/ebastine/rupatadine adverse reactions , dose reduction of bilastine/ebastine/rupatadine may be necessary.
Mizolastine	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of mizolastine-related adverse reactions, such as QT prolongation.
Terfenadine	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	Use with caution, monitor for eletriptan adverse reactions , dose reduction of eletriptan may be necessary.
Ergot alkaloids	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism.

Antineoplastics	
Bortezomib Brentuximab vedotin Busulfan Erlotinib Gefitinib Imatinib Ixabepilone Nintedanib Panobinostat Ponatinib Ruxolitinib Sonidegib Vandetanib	Use with caution, monitor for adverse reactions related to the antineoplastic drug , dose reduction of the antineoplastic drug may be necessary.
Idelalisib	Use with caution, monitor for adverse reactions related to itraconazole and/or idelalisib, dose reduction of itraconazole and/or idelalisib may be necessary.
Axitinib Bosutinib Cabazitaxel Cabozantinib Ceritinib Cobimetinib Crizotinib Dabrafenib Dasatinib Docetaxel Ibrutinib Lapatinib Nilotinib Olaparib Pazopanib Sunitinib Trabectedin Trastuzumab emtansine Vinca alkaloids	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the antineoplastic drug
Regorafenib	Not recommended during and for 2 weeks after treatment with itraconazole. Regorafenib efficacy may be reduced.
Irinotecan	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of irinotecan-related adverse reactions, such as potentially life-threatening myelosuppression and diarrhea.
Antipsychotics, Anxiolytics and Hypnotics	
Alprazolam Aripiprazole Brotizolam Buspirone Cariprazine Haloperidol Midazolam (iv) Perospirone Quetiapine Ramelteon Risperidone Suvorexant Zopiclone	Use with caution, monitor for adverse reactions related to the antipsychotic, anxiolytic or hypnotic drug, dose reduction of these drugs may be necessary.
Lurasidone	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)	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	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	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of sertindole-related adverse reactions, such as QT prolongation and TdP.
Triazolam	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of triazolam-related adverse reactions, such as seizures, respiratory depression, angioedema, apnea and coma.
Antivirals	
Asunaprevir (boosted) Tenofovir disoproxil fumarate (TDF)	Use with caution,
Boceprevir	Use with caution, monitor for adverse reactions related to itraconazole and/or boceprevir, dose reduction of itraconazole may be necessary. Refer to the boceprevir label for specific actions to be taken.
Cobicistat	Use with caution, monitor for adverse reactions related to itraconazole, dose reduction of itraconazole may be necessary.
Daclatasvir Vaniprevir	Use with caution, monitor for daclatasvir/vaniprevir adverse reactions , dose reduction of daclatasvir/vaniprevir may be necessary.
Darunavir (boosted) Fosamprenavir (ritonavir-boosted) Telaprevir	Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
Elvitegravir (boosted)	Use with caution, monitor for adverse reactions related to itraconazole and/or elvitegravir (ritonavir-boosted). Dose reduction of itraconazole may be necessary; refer to the elvitegravir label for specific actions to be taken.
Efavirenz Nevirapine	Not recommended from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Elbasvir/Grazoprevir	Use with caution, monitor for adverse reactions related to the co-administered drugs
Glecaprevir /Pibrentasvir	Use with caution, monitor for adverse reactions related to the co-administered drugs
Indinavir	Use with caution, monitor for adverse reactions related to itraconazole and/or indinavir, dose reduction of itraconazole and/or indinavir may be necessary.
Maraviroc	Use with caution monitor for adverse reactions. Dose reduction of maraviroc may be necessary.
Ombitasvir/ Paritaprevir/ Ritonavir with or without Dasabuvir	Use with caution. Monitor for adverse reactions related to itraconazole and or the antivirals, dose reduction of itraconazole may be necessary.
Ritonavir	Use with caution, monitor for adverse reactions related to itraconazole and/or ritonavir, Dose reduction of itraconazole may be necessary; refer to the ritonavir label for specific actions to be taken.
Saquinavir	Use with caution, monitor for adverse reactions related to itraconazole and/or saquinavir, Dose reduction of itraconazole may be necessary; refer to the saquinavir label for specific actions to be taken.
Simeprevir	Not recommended during and for 2 weeks after treatment with itraconazole.
Beta Blockers	
Nadolol	Use with caution, monitor for nadolol adverse reactions. Dose reduction of nadolol may be necessary.
Calcium Channel Blockers	
Bepridil	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	Use with caution, monitor for adverse reactions related to itraconazole and/or diltiazem, dose reduction of itraconazole and/or diltiazem may be necessary.
Felodipine Lercanidipine Nisoldipine	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	Use with caution, monitor for dihydropyridine/verapamil adverse reactions, dose reduction of dihydropyridine/verapamil may be necessary.
Cardiovascular Drugs, Miscellaneous	
Aliskiren Riociguat Sildenafil (pulmonary hypertension) Tadalafil (pulmonary hypertension)	Not recommended during and for 2 weeks after treatment with itraconazole Increased risk of adverse reactions related to the cardiovascular drug.
Bosentan Guanfacine	Use with caution, monitor for bosentan/guanfacine adverse reactions, dose reduction of bosentan/guanfacine may be necessary.
Ivabradine	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	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	Use with caution, monitor for contraceptive adverse reaction, refer to the dienogest/ulipristal label for specific actions to be taken.
Diuretics	
Eplerenone	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of eplerenone-related adverse reactions, such as hyperkalemia and hypotension.
Gastrointestinal Drugs	
Aprepitant Loperamide Netupitant	Use with caution, monitor for aprepitant/loperamide/netupitant adverse reactions Dose reduction of aprepitant/loperamide/ may be necessary. Refer to the netupitant label for specific actions to be taken.
Cisapride	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	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	Use with caution
Naloxegol	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of naloxegol-related adverse reactions, such as opioid withdrawal symptoms.
Saccharomyces boulardii	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	Use with caution, monitor for immunosuppressant adverse reactions, Dose reduction of the immunosuppressant drug may be necessary
Everolimus Sirolimus (rapamycin)	Not recommended during and for 2 weeks after treatment with itraconazole Increased risk of everolimus/ sirolimus-related adverse reactions.
Lipid Regulating Drugs	
Atorvastatin	Use with caution, monitor for atorvastatin adverse reactions, Dose reduction of atorvastatin may be necessary.
Lomitapide	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	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	Use with caution, monitor for reduced efficacy of meloxicam, dose adaption of meloxicam may be necessary.
Respiratory Drugs	
Salmeterol	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of salmeterol-related adverse reactions
SSRIs, Tricyclics and Related Antidepressants	
Reboxetine Venlafaxine	Use with caution, monitor for reboxetine/venlafaxine adverse reactions , dose reduction of reboxetine/venlafaxine may be necessary.
Urologic Drugs	
Avanafil	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	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	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of darifenacin/vardenafil-related adverse reaction
Dutasteride Imidafenacin Oxybutynin Sildenafil (erectile dysfunction) Tadalafil (erectile dysfunction and benign prostatic hyperplasia) Tolterodine Udenafil	Use with caution, monitor for urologic drug adverse reactions, dose reduction of the urologic drug may be necessary; refer to the dutasteride label for specific actions to be taken.
Fesoterodine	Contraindicated in patients with moderate to severe renal or hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of fesoterodine-related adverse reactions, such as severe anticholinergic effects. Use with caution in other patients: monitor for fesoterodine adverse reactions, dose reduction of fesoterodine may be necessary.
Solifenacin	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 dose reduction of solifenacin may be necessary.
Miscellaneous Drugs and Other Substances	
Alitretinoin (oral) Cabergoline Cannabinoids Cinacalcet	Use with caution, monitor for alitretinoin/ cabergoline/cannabinoids/cinacalcet drug adverse reactions, dose reduction of alitretinoin/ cabergoline/cannabinoids/cinacalcet may be necessary
Colchicine	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 suppression. Not recommended in other patients, during and and for 2 weeks after treatment with itraconazole. Increased risk of colchicine related adverse reactions
Eliglustat	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 AEs 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, dose reduction of eliglustat may be necessary.
Ergot alkaloids	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism.
Galantamine	Use with caution. Monitor for Galantamine adverse reactions. Dose reduction of galantamine may be necessary
Ivacaftor	Use with caution, monitor for ivacaftor adverse reactions, dose reduction of ivacaftor may be necessary.
Lumacaftor/Ivacaftor	Not recommended from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of ivacaftor-related adverse reactions.
Vasopressin Receptor Antagonists	
Conivaptan Tolvaptan	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of conivaptan/ tolvaptan-related adverse reactions.
Mozavaptan	Use with caution, monitor for mozavaptan adverse reactions, dose reduction of mozavaptan may be necessary.

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. 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.

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

Table 1: Adverse Reactions Reported by ≥1% of Patients Treated with SPORANOX Capsules

System Organ Class Adverse Reaction	SPORANOX Capsules % (N=8499)
Nervous System Disorders	
Headache	1.6
Gastrointestinal Disorders	
Nausea	1.6
Abdominal pain	1.3

Table 2: Adverse Reactions Reported by <1% of Patients Treated with SPORANOX Capsules

System Organ Class: 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
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: Headache, Vomiting, Abdominal pain, Diarrhoea, Hepatic function abnormal, Hypotension, Nausea, and Urticaria.
Table 3: Adverse Reactions Identified During Post-Marketing Experience with SPORANOX
Immune System Disorders: *Very rare* - Serum sickness, Angioneurotic edema, Anaphylactic reaction
Metabolism and Nutrition Disorders: *Very rare* - Hypertriglyceridemia
Nervous System Disorders: *Very rare* - Tremor
Eye Disorders: *Very rare* - Visual disturbances (including diplopia and vision blurred)
Ear and Labyrinth Disorders: *Very rare* - Transient or permanent hearing loss
Cardiac Disorders: *Very rare* - Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders: *Very rare* - Dyspnea
Gastrointestinal Disorders: *Very rare* - Pancreatitis
Hepatobiliary Disorders: *Very rare* - Serious hepato-toxicity (including some cases of fatal acute liver failure)
Skin and Subcutaneous Tissue Disorders: *Very rare* - Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalized exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Investigations: *Very rare* - 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.

PHARMACEUTICAL PARTICULARS
Shelf Life: Observe expiry date on the outer pack.
Special Precautions for Storage: Store between 15 and 30° C. Keep all medicines out of reach of children. Protect from light and moisture.
Nature and Contents of Container: Sporanox 100mg (itraconazole) in a pellet formulation is supplied in blister pack of 4 capsules.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۱۵ سے ۳۰ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Aspin Pharma (Pvt) Ltd.,
Plot No. 10 & 25, Sector No. 20, Korangi Industrial Area, Karachi-74900, Pakistan.

ASPIN
An OBS Group Company