**PROFESSIONAL INFORMATION**

## SCHEDULING STATUS

Schedule 4

## 1. NAME OF THE MEDICINE

TRISPORAL 100 mg Capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg of itraconazole in a pellet formulation.

Contains sugar (sucrose): each capsule contains 175.68 mg of sucrose.

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Capsule

Pink and blue capsules (size 0) containing white to faintly cream-coloured beads (pellets).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

TRISPORAL capsules are indicated for:

1) Treatment of vulvovaginal candidiasis

2) Treatment of dermatomycosis, including highly keratinised regions as in plantar *tinea pedis* and palmar *tinea manus,* which does not respond to conventional therapy.

3) Onychomycosis caused by dermatophytes and/or yeasts and which does not respond to other therapy.

4) Although proof of efficacy is limited, TRISPORAL capsules have been used in systemic aspergillosis and candidiasis, histoplasmosis, sporotrichosis, paracoccidioidomycosis and blastomycosis. However, due to the potential of significant interactions with many medicines, TRISPORAL should be used in cases resistant to other antifungal medicines.

### 4.2 Posology and method of administration

TRISPORAL capsules should be taken immediately after a meal for optimal absorption.

The capsules must be swallowed whole.

Dosage recommendations vary according to the infection treated:

| Indication | Dose | Median treatment duration |
|---|---|---|
| • Treatment of vulvovaginal candidiasis | 200 mg twice daily<br>or<br>200 mg once daily | 1 day<br>or<br>3 days |
| • Treatment of dermatomycosis | 200 mg once daily<br>or | 7 days<br>or |

| | | |
|---|---|---|
| | 100 mg once daily | 15 days |
| • Treatment of dermatomycosis in highly keratinised 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 onychomycosis<br>Prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis | | |
| (continuous treatment) | 200 mg once daily | 3 months |
| (pulse treatment) | 200 mg twice daily | 1 week<br>Fingernail infections: 2 pulse treatments<br>Toenail infections: 3 pulse treatments.<br>Pulse treatments are always separated by a 3-week medicine-free interval. See table below. |

| **Site of onychomycosis** | **Week 1** | **Weeks 2, 3 and 4** | **Week 5** | **Weeks 6, 7 and 8** | **Week 9** |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Toenails with or without fingernail involvement | **Pulse 1** 200 mg twice daily | Itraconazole free weeks | **Pulse 2** 200 mg twice daily | Itraconazole free weeks | **Pulse 3** 200 mg twice daily |
| Fingernails only | **Pulse 1** 200 mg twice daily | Itraconazole free weeks | **Pulse 2** 200 mg twice daily | | |

Dosages that have been used in systemic mycoses:

| **SYSTEMIC MYCOSES** | | | |
|---|---|---|---|
| **Indication** | **Dose** | **Median treatment duration*** | **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 candidiasis (*excluding vulvovaginal*) | 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 histoplasmosis (*excluding meningeal histoplasmosis*) | 200 mg once daily - 200 mg twice daily *(or 400 mg once daily)* | 8 months | |
| Treatment of sporotrichosis (lymphocutaneous and cutaneous) | 100 mg once daily | 3 months | |
| Treatment of paracoccidioidomycosis | 100 mg once daily | 6 months | Data on the efficacy of TRISPORAL capsules at this dosage for treatment of paracoccidioidomycosis in patients with HIV is not available. |
| Treatment of chromomycosis | 100 - 200 mg once daily | 6 months | |
| Treatment of blastomycosis | 100 mg once daily - 200 mg twice daily (*or 400 mg once daily*) | 6 months | |

** The duration of treatment should be adjusted depending on the clinical response.*

Changes in the international and local antimicrobial resistance patterns should also be a consideration. Principles of antimicrobial stewardship should be adhered to.

**Special Populations**

***Paediatrics***

Clinical data on the use of TRISPORAL capsules in paediatric patients are limited.

The use of TRISPORAL capsules in paediatric patients is not recommended (see section 4.4).

***Elderly***

Clinical data on the use of TRISPORAL capsules in elderly patients are limited.

***Hepatic impairment***

Limited data are available on the use of TRISPORAL in patients with hepatic impairment. Caution should be exercised when TRISPORAL 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 TRISPORAL may be lower in patients with renal insufficiency. Caution should be exercised when TRISPORAL is administered in this patient population and adjusting the dose may be considered.

Data from a small number of HIV-infected patients suggested that the response rate of histoplasmosis in HIV-infected patients is similar to non-HIV-infected patients. The clinical course of histoplasmosis in HIV-infected patients is more severe and usually requires maintenance therapy to prevent relapse. The optimal dosage regimen for treatment and

maintenance therapy are unknown. Studies to investigate the efficacy and safety of TRISPORAL, including optimal dosage and duration in HIV-infected patients are ongoing.

## 4.3 Contraindications

TRISPORAL capsules are contraindicated in pregnant and breastfeeding women. Women of childbearing potential using TRISPORAL capsules should use barrier contraceptives until the next menstrual period following the end of TRISPORAL therapy (see section 4.6).

TRISPORAL capsules are contraindicated in patients with a known hypersensitivity to itraconazole, other azole antifungal agents or any of the excipients.

**Co-administration of a number of CYP3A4 substrates is contraindicated with TRISPORAL capsules. Increased plasma concentrations of these medicines, caused by coadministration with TRISPORAL, may increase or prolong both therapeutic and adverse effects that might be life-threatening. For example, increased plasma concentrations of some of these medicines can lead to QT prolongation and ventricular tachydysrhythmias including occurrences of torsade de pointes, a potentially fatal dysrhythmia. Specific examples are listed in section 4.5.**

- Examples of medicines that are contraindicated for use with TRISPORAL are (also see section 4.5):
  - *Analgesics:* levacetylmethadol (levomethadyl), methadone
  - *Antidysrhythmics:* disopyramide, dofetilide, dronedarone, quinidine
  - *Antibacterials:* telithromycin, in subjects with severe renal impairment or severe hepatic impairment
  - *Anticoagulants and Antiplatelet Medicine:* ticagrelor
  - *Antihelminthics, Antifungals and Antiprotozoals:* halofantrine, isavuconazole
  - *Antihistamines: astemizole*, mizolastine, terfenadine
  - *Antimigraine Medicines:* ergot alkaloids such as dihydroergotamine, ergometrine, ergotamine, methylergometrine
  - *Antineoplastics:* irinotecan
  - *Antipsychotics, Anxiolytics and Hypnotics*: lurasidone, oral midazolam, pimozide, sertindole, triazolam
  - *Calcium Channel Blockers*: bepridil, felodipine, lercanidipine, nisoldipine
  - *Cardiovascular Medicines, Miscellaneous:* ivabradine, ranolazine
  - *Diuretics:* eplerenone
  - *Gastrointestinal Medicines:* cisapride, domperidone, naloxegol
  - *Lipid Regulating Medicines:* lomitapide, lovastatin, simvastatin
  - *Urologic Medicines:* avanafil, dapoxetine, fesoterodine, in patients with moderate to severe renal impairment;
    solifenacin, in subjects with severe renal impairment or moderate to severe hepatic impairment

- *Miscellaneous Medicines and Other Substances:* colchicine, in patients with renal or hepatic impairment, eliglustat, ergot alkaloids (see *Antimigraine medicines)*

TRISPORAL capsules are contraindicated in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening systemic fungal infections (see section 4.4).

TRISPORAL has been shown to have no benefit in the prophylaxis of cryptococcal meningitis in HIV infected patients.

## 4.4 Special warnings and precautions for use

***Cardiac effects***

In a healthy volunteer study with TRISPORAL 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.

TRISPORAL has been shown to have a negative inotropic effect and TRISPORAL 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 TRISPORAL.

TRISPORAL 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 ischaemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other oedematous 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, TRISPORAL should be discontinued.

***Interaction potential***

Coadministration of specific medicines with itraconazole may result in changes in efficacy of itraconazole and/or the co-administered medicine, life-threatening effects and/or sudden death. Medicines that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in section 4.3 and section 4.5.

***Porphyria***

There are no data available for use of TRISPORAL in patients with porphyria and therefore should be used with caution.

***Cross-hypersensitivity***

The limited information regarding cross-hypersensitivity between TRISPORAL and other azole antifungal agents indicates that caution should be used in prescribing TRISPORAL capsules to patients with hypersensitivity to other azoles.

***Neuropathy***

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

***Hearing Loss***

Transient and permanent hearing loss has been reported in patients receiving treatment with TRISPORAL. Several of these reports included concurrent administration of quinidine which is contraindicated (see section 4.3). The hearing loss usually resolves when treatment is stopped but can persist in some patients.

***Cross-resistance***

In systemic candidiasis, 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 TRISPORAL therapy.

***Interchangeability***

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

***Hepatic effects***

Cases of serious, usually reversible idiosyncratic hepatitis, which may be fatal, have been observed.

**Serious hepatotoxicity, including cases of fatal acute liver failure, has occurred with the use of TRISPORAL. 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 medicines. Some patients had no obvious risk factors for liver disease. These cases have been observed within the first week of treatment and up to 1½ years after continuous use of TRISPORAL.**

Liver function monitoring is recommended in patients receiving TRISPORAL treatment. Patients should be instructed to promptly report to their medical practitioner 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 TRISPORAL is administered in this patient population. It is recommended that patients with impaired hepatic function be carefully monitored when taking TRISPORAL. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with TRISPORAL capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolised by CYP3A4.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other medicines, treatment with TRISPORAL is strongly discouraged. 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 medicines.

***Reduced gastric acidity***

Absorption of itraconazole from TRISPORAL capsules is impaired when the 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 medicines that reduce gastric acidity), it is advisable to administer TRISPORAL 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 section 4.5).

***Paediatrics***

Clinical data on the use of TRISPORAL capsules in paediatric patients are limited. The use of TRISPORAL capsules in paediatric patients is not recommended.

***Elderly***

Clinical data on the use of TRISPORAL capsules in elderly patients are limited.

***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 patients with renal insufficiency. Caution should be exercised when TRISPORAL is administered in this patient population and adjusting the dose may be considered.

***Immunocompromised patients***

In some immunocompromised patients (e.g., neutropenic, human immunodeficiency virus (HIV) infected or organ transplant patients), the oral bioavailability of TRISPORAL 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, TRISPORAL capsules are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

***Patients with HIV infection***

In patients with HIV infection having received treatment for a systemic fungal infection and who are considered at risk for relapse, the treating medical practitioner should evaluate the need for maintenance treatment.

Because hypochlorhydria has been reported in HIV-infected individuals, the absorption of itraconazole in these patients may be decreased.

***Cystic fibrosis***

In cystic fibrosis patients, a high interindividual variability in 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 only 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 TRISPORAL capsules, consideration should be given to switching to an alternative therapy.

***Sucrose***

TRISPORAL contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take TRISPORAL capsules.

Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

## 4.5 Interaction with other medicines and other forms of interaction

Itraconazole is a medicine 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 medicines that may interact with itraconazole, organized per medicine family for easy reference. This list of examples is not comprehensive and therefore the label of each medicine that is co-administered 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 co-administration.

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Co-administration 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. Co-administration 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. Medicines 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 medicines that reduce gastric acidity (see section 4.4).

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

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 medicines whose metabolism is affected by itraconazole.
The following general recommendations apply, unless stated differently in table.

- Contraindicated': Under no circumstances is the medicine to be co-administered 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 section 4.3)

- Not recommended': It is recommended that the use of the medicine be avoided, unless the benefits outweigh the potentially increased risks. If co-administration cannot be avoided, clinical monitoring is recommended, and the dosage of itraconazole and/or the co-administered medicine 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 medicine is co-administered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely and the dosage of itraconazole and/or the co-administered medicine adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Medicines that reduce gastric acidity (itraconazole caps 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

Examples of interacting medicines are listed in the table below. The medicines listed in this table are based on either medicine interaction studies or case reports, or potential interactions based on the mechanism of interaction.

| Medicinal products within class | Clinical comment<br>(see above for additional info) |
|---|---|
| **Alpha Blockers** | |
| Alfuzosin<br>Silodosin<br>Tamsulosin | 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 | Use with caution, monitor for adverse reactions related to the analgesic[c], 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[c]. |
| Levacetylmethadol (levomethadyl) | 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. |
| **Antidysrhythmics** | |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Digoxin | Use with caution, monitor for digoxin adverse reactions, dose reduction of digoxin may be necessary[c]. |
| Disopyramide | Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of disopyramide-related adverse reactions, such as serious dysrhythmias including TdP. |
| Dofetilide | Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of dofetilide-related adverse reactions, such as serious ventricular dysrhythmias 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 |

| Medicinal products within class | Clinical comment<br>(see above for additional info) |
|---|---|
| | not recommended: increased risk of bedaquiline-related adverse reactions[c]. |
| Ciprofloxacin<br>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[c], dose reduction of itraconazole and/or clarithromycin may be necessary . |
| Delamanid<br>Trimetrexate | Use with caution, monitor for delamanid/trimetrexate adverse reactions, dose reduction of delamanid/trimetrexate may be necessary[c]. |
| Isoniazid<br>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[c]. |
| Telithromycin | Contraindicated in patients with severe renal or hepatic impairment during and for 2 weeks after |

| Medicinal products within class | Clinical comment<br>(see above for additional info) |
|---|---|
| | treatment with itraconazole, Increased risk of telithromycin-related adverse reactions, 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[c]. |
| **Anticoagulants and Antiplatelet Medicines** | |
| Apixaban<br>Rivaroxaban<br>Vorapaxar | Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of apixaban/rivaroxaban/vorapaxar-related adverse reactions[c]. |
| Coumarins (eg, warfarin)<br>Cilostazol | Use with caution, monitor for coumarins/cilostazol adverse reactions, dose reduction of coumarins/cilostazol may be necessary[c]. |
| Dabigatran | Use with caution, monitor for dabigatran adverse reactions, dose reduction of dabigatran may be necessary[c]. |
| Ticagrelor | Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ticagrelor-related adverse reactions, such as bleeding. |
| **Anticonvulsants** | |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Carbamazepine | 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><br>Phenytoin | Not recommended from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced . |
| Antidiabetics | |
| Repaglinide<br><br>Saxagliptin | Use with caution, monitor for repaglinide/saxagliptin adverse reactions, dose reduction of repaglinide/saxagliptin may be necessary[c]. |
| **Antihelminthics, antifungals and antiprotozoals** | |
| Artemether-lumefantrine<br><br>Quinine | Use with caution, monitor for artemether-lumefantrine/quinine adverse reactions[c]. Refer to the label for specific actions to be taken. |
| Halofantrine | Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of halofantrine-related adverse reactions, such as QT prolongation and fatal dysrhythmias. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| 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[c]. |
| **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 dysrhythmias. |
| Bilastine<br>Ebastine<br>Rupatadine | Use with caution, monitor for bilastine/ebastine/rupatadine adverse reactions[c], 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. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| 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 dysrhythmias. |
| **Antimigraine Medicines** | |
| Eletriptan | Use with caution, monitor for eletriptan adverse reactions[c], dose reduction of eletriptan may be necessary. |
| Ergot alkaloids (such as dihydroergotamine, ergometrine, ergotamine, methylergometrine) | 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 | Use with caution, monitor for adverse reactions related to the antineoplastic medicines[c], dose reduction of the antineoplastic medicine may be necessary. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Ponatinib<br><br>Ruxolitinib<br><br>Sonidegib<br><br>Vandetanib | |
| Idelalisib | 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><br>Bosutinib<br><br>Cabazitaxel<br><br>Cabozantinib<br><br>Ceritinib<br><br>Cobimetinib<br><br>Crizotinib<br><br>Dabrafenib<br><br>Dasatinib<br><br>Docetaxel<br><br>Ibrutinib<br><br>Lapatinib<br><br>Nilotinib<br><br>Olaparib<br><br>Pazopanib | Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the antineoplastic medicine[c].<br><br>Additionally:<br><br>For cabazitaxel, even though the change in pharmacokinetic parameters did not reach statistical significance in a low-dose medicine interaction study with ketoconazole, a high variability in the results was observed.<br><br>For ibrutinib, refer to the label for specific actions to be taken. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Sunitinib<br><br>Trabectedin<br><br>Trastuzumab emtansine<br><br>Vinca alkaloids | |
| 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 diarrhoea. |
| **Antipsychotics, Anxiolytics and Hypnotics** | |
| Alprazolam<br><br>Aripiprazole<br><br>Brotizolam<br><br>Buspirone<br><br>Cariprazine<br><br>Haloperidol<br><br>Midazolam (iv)<br><br>Perospirone<br><br>Quetiapine | Use with caution, monitor for adverse reactions related to the antipsychotic, anxiolytic or hypnotic medicines[c], dose reduction of these medicines may be necessary. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Ramelteon<br><br>Risperidone<br><br>Suvorexant<br><br>Zopiclone | |
| 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 dysrhythmias, 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. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| 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)<br><br>Tenofovir disoproxil fumarate (TDF) | Use with caution, however, refer to the label of the antiviral medicine for specific actions to be taken. |
| Boceprevir | 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 | Use with caution, monitor for adverse reactions related to itraconazole, dose reduction of itraconazole may be necessary. |
| Daclatasvir<br><br>Vaniprevir | Use with caution, monitor for daclatasvir/vaniprevir adverse reactions[c], dose reduction of daclatasvir/vaniprevir may be necessary. |
| Darunavir (boosted)<br><br>Fosamprenavir (ritonavir-boosted)<br><br>Telaprevir | Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Elvitegravir (boosted) | Use with caution, monitor for adverse reactions related to itraconazole and/or elvitegravir (ritonavir-boosted) [c]. Dose reduction of itraconazole may be necessary; refer to the elvitegravir label for specific actions to be taken. |
| Efavirenz<br><br>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 medicines[c]. Refer to the elbasvir/grazoprevir label for specific actions to be taken. |
| Glecaprevir/Pibrentasvir | Use with caution, monitor for adverse reactions related to the co-administered medicines[c]. Refer to the glecaprevir/pibrentasvir label for specific actions to be taken. |
| Indinavir | 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 | Use with caution monitor for adverse reactions[c]. Dose reduction of maraviroc may be necessary. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir | 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 co-administered medicines for specific actions to be taken. |
| Ritonavir | 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 | 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. |
| Simeprevir | Not recommended during and for 2 weeks after treatment with itraconazole. |
| **Beta Blockers** | |
| Nadolol | Use with caution, monitor for nadolol adverse reactions[c]. Dose reduction of nadolol may be necessary. |
| **Calcium Channel Blockers** | |
| Bepridil | Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of |

| Medicinal products within class | Clinical comment<br>(see above for additional info) |
|---|---|
| | bepridil-related adverse reactions, such as new dysrhythmias and TdP type ventricular tachycardia. |
| Diltiazem | 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 | 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>Verapamil | Use with caution, monitor for dihydropyridine/verapamil adverse reactions[c], dose reduction of dihydropyridine/verapamil may be necessary. |
| **Cardiovascular Medicines, Miscellaneous** | |
| Aliskiren<br>Riociguat<br>Sildenafil (pulmonary hypertension)<br>Tadalafil (pulmonary hypertension) | Not recommended during and for 2 weeks after treatment with itraconazole[c]. Increased risk of adverse reactions related to the cardiovascular medicine. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Bosentan<br><br>Guanfacine | Use with caution, monitor for bosentan/guanfacine adverse reactions[c], 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<br><br>Ulipristal | Use with caution, monitor for contraceptive adverse reactions[c], 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 hyperkalaemia and hypotension. |
| **Gastrointestinal Medicines** | |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Aprepitant<br><br>Loperamide<br><br>Netupitant | Use with caution, monitor for aprepitant/loperamide/netupitant adverse reactions[c], Dose reduction of aprepitant/loperamide/ may be necessary. Refer to the netupitant label for specific actions to be taken. |
| Cisapride | 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 dysrhythmias and TdP. |
| Domperidone | Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of domperidone-related adverse reactions, such as serious ventricular dysrhythmias and sudden cardiac death. |
| Medicines that reduce gastric acidity | Use with caution: Medicines that reduce gastric acidity: e.g. acid neutralizing medicines such as aluminium hydroxide, or acid secretion suppressors such as H2- receptor antagonists and proton pump inhibitors.<br><br>When co-treatment with acid neutralizing medicines (e.g. aluminium hydroxide) these should |

| Medicinal products within class | Clinical comment<br>(see above for additional info) |
|---|---|
| | be administered at least 2 hours before or 2 hours after the intake of TRISPORAL capsules. |
| 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<br>Ciclesonide<br>Cyclosporine<br>Dexamethasone<br>Fluticasone<br>Methylprednisolone<br>Tacrolimus<br>Temsirolimus | Use with caution monitor for immunosuppressant adverse reactions[c], Dose reduction of the immunosuppressant medicine may be necessary. |
| Everolimus<br>Sirolimus (rapamycin) | Not recommended during and for 2 weeks after treatment with itraconazole[c]. Increased risk of everolimus/ sirolimus-related adverse reactions. |

| Medicinal products within class | Clinical comment<br>(see above for additional info) |
|---|---|
| | |
| **Lipid Regulating Medicines** | |
| Atorvastatin | Use with caution, monitor for atorvastatin adverse reactions[c], 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<br>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 Medicines** | |
| Meloxicam | Use with caution, monitor for reduced efficacy of meloxicam, dose adaption of meloxicam may be necessary. |
| **Respiratory Medicines** | |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Salmeterol | 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><br>Venlafaxine | Use with caution, monitor for reboxetine/venlafaxine adverse reactions[c], dose reduction of reboxetine/venlafaxine may be necessary. |
| **Urologic Medicines** | |
| 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<br><br>Vardenafil | Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of darifenacin/vardenafil-related adverse reactions[c]. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| Dutasteride<br>Imidafenacin<br>Oxybutynin<br>Sildenafil (erectile dysfunction)<br>Tadalafil (erectile dysfunction and benign prostatic hyperplasia)<br>Tolterodine<br>Udenafil | Use with caution, monitor for urologic medicine adverse reactions[c], dose reduction of the urologic medicine may be necessary; refer to the dutasteride label for specific actions to be taken.<br>(For sildenafil and tadalafil, see also *Cardiovascular Medicines, Miscellaneous Medicines and other substances*.) |
| 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.<br>Use with caution in other patients: monitor for fesoterodine adverse reactions[c], 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. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| | Use with caution in other patients, monitor for solifenacin adverse reactions[c], dose reduction of solifenacin may be necessary. |
| **Miscellaneous Medicines and Other Substances** | |
| Alitretinoin (oral)<br>Cabergoline<br>Cannabinoids<br>Cinacalcet | Use with caution, monitor for alitretinoin/ cabergoline/cannabinoids/cinacalcet medicine adverse reactions, dose reduction of alitretinoin/ cabergoline/cannabinoids/cinacalcet may be necessary[c]. |
| 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 dysrhythmias, 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 | Contraindicated in CYP2D6 EMs taking a strong or moderate CYP2D6 inhibitor / CYP2D6 IMs and PMs, during and for 2 weeks after treatment with |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| | itraconazole. Increased risk of eliglustat-related adverse reactions such as prolongation of the PR, QTc, and/or QRS cardiac interval, and cardiac dysrhythmias.<br>Use with caution in CYP2D6 EMs, monitor for eliglustat adverse reactions[c], 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.<br>(see also *Antimigraine Medicines*) |
| Galantamine | Use with caution, monitor for ivacaftor adverse reactions[c], dose reduction of galantamine may be necessary. |
| Ivacaftor | Use with caution, monitor for ivacaftor adverse reactions[c], 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[c]. |

| Medicinal products within class | Clinical comment<br><br>(see above for additional info) |
|---|---|
| **Vasopressin Receptor Antagonists** | |
| Conivaptan<br><br>Tolvaptan | Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of conivaptan/ tolvaptan-related adverse reactions[c]. |
| Mozavaptan | Use with caution, monitor for mozavaptan adverse reactions[c], dose reduction of mozavaptan may be necessary. |

*CYP3A4 inhibitors (including itraconazole) may increase systemic contraceptive hormone concentrations.

EMs: extensive metabolisers; IMs: intermediate metabolisers, PMs: poor metabolisers; TdP: Torsade de Pointes

[c] Please consult the corresponding label for information on medicine-related adverse events

**Pediatric population**

Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*

TRISPORAL is contraindicated during pregnancy (see section 4.3).

There is limited information on the use of TRISPORAL during pregnancy.

During post-marketing experience, cases of congenital abnormalities have been reported. These cases include skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations.

A causal relationship with TRISPORAL has not been established.

TRISPORAL has been shown to cross the placenta in the rat model. In animal studies itraconazole has shown to be teratogenic.

*Women of childbearing potential*

Women of childbearing potential taking TRISPORAL capsules should use contraceptive precautions. Highly effective contraception should be continued until the menstrual period following the end of TRISPORAL capsule therapy (see section 4.5).

*Breastfeeding*

Itraconazole is excreted in human milk. The patient should not breastfeed.

*Fertility*

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

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss (see section 4.8.), which may occur in some instances, must be taken into account.

## 4.8 Undesirable effects

*Summary of the safety profile*

The most frequently reported adverse drug reactions (ADRs) with TRISPORAL capsules treatment identified from clinical trials and/or from spontaneous reporting were headache, abdominal pain, and nausea. The most serious ADRs were serious allergic reactions, cardiac failure/congestive heart failure/pulmonary oedema, pancreatitis, serious hepatotoxicity (including some cases of fatal acute liver failure), and serious skin reactions. Refer to subsections *Clinical Trials* and *Post marketing experience* for the frequencies and for other observed ADRs. Refer to section 4.4 *Special warnings and precautions for use* for additional information on other serious effects.

*Clinical trials*

The safety of TRISPORAL capsules was evaluated in 8 499 patients who participated in 107 open-label and double-blind clinical trials in patients with fungal infections. Of the 8 499 patients treated with TRISPORAL capsules, 2 104 patients were treated with TRISPORAL capsules during double-blind trials. Adverse reactions reported for–patients treated with TRISPORAL capsules in these clinical trials are shown in Table 1.

Adverse reactions are listed by system organ class and frequency. The following terms and frequencies are applied: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

**Table 1: Adverse reactions reported by patients treated with TRISPORAL capsules in clinical trials**

| System Organ Class<br>*Frequency Category* | Adverse Reaction |
|---|---|
| **Blood and Lymphatic System Disorders**<br>*Rare* | Leukopenia |
| **Immune System Disorders**<br>*Uncommon* | Hypersensitivity |
| **Infections and Infestations**<br>*Uncommon* | Rhinitis, sinusitis, upper respiratory tract infection |
| **Nervous System Disorders**<br>*Common*<br>*Rare* | Hypersensitivity<br>Dysgeusia, hypoesthesia, paraesthesia |
| ***Ear and Labyrinth Disorders***<br>*Rare* | Tinnitus |
| ***Gastrointestinal Disorders***<br>*Common*<br>*Uncommon* | Nausea, abdominal pain<br>Constipation, diarrhoea, dyspepsia, flatulence, vomiting |
| ***Hepatobiliary Disorders***<br>*Uncommon*<br>*Rare* | Abnormal hepatic function<br>Hyperbilirubinemia |
| ***General Disorders and Administration Site Conditions***<br>*Rare* | Oedema |
| ***Skin and Subcutaneous Tissue Disorders***<br>*Uncommon* | Pruritis, rash, urticaria |

| | |
|---|---|
| ***Reproductive System and Breast Disorders*** | |
| *Uncommon* | Menstrual disorder |
| *Rare* | Erectile dysfunction |
| ***Renal and Urinary Disorders*** | |
| *Rare* | Pollakiuria |

The following is a list of additional adverse reactions associated with itraconazole that have been reported in clinical trials of itraconazole oral solution and/or itraconazole given IV, excluding the adverse reaction “Injection site inflammation” which is specific to the injection route of administration.

**Blood and Lymphatic System Disorders:** Granulocytopaenia, thrombocytopaenia

**Immune System Disorders:** Anaphylactoid reaction

**Metabolism and Nutrition Disorders:** Hyperglycaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia

**Psychiatric Disorders:** Confusional state

**Nervous System Disorders:** Peripheral neuropathy, dizziness, somnolence

**Cardiac Disorders:** Cardiac failure, left ventricular failure, tachycardia

**Vascular Disorders:** Hypertension, hypotension

**Respiratory, Thoracic and Mediastinal Disorders:** Pulmonary oedema, dysphonia, cough

**Gastrointestinal Disorders:** Gastrointestinal disorder

**Hepatobiliary Disorders:** Hepatic failure, hepatitis, jaundice

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

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

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

**General Disorders and Administration Site Conditions:** Generalised oedema, face oedema, chest pain, pyrexia, pain, fatigue, chills

**Investigations:** Increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood alkaline phosphatase (ALP), increased blood lactate dehydrogenase (LDH), increased blood urea, increased gamma-glutamyltransferase (GGT), increased hepatic enzyme and abnormal urine analysis.

***Post marketing experience***

Adverse reactions from spontaneous reports during the worldwide post marketing experience with TRISPORAL are included in Table 2.

**Table 2. Post marketing reports of adverse reactions**.

| System organ class |
| --- |
| **Immune system disorders**<br><br>Serum sickness, angioedema, anaphylactic shock reaction |
| **Metabolism and nutrition disorders**<br><br>Hypertriglyceridemia |
| **Nervous system disorders**<br><br>Tremor |
| **Eye disorders**<br><br>Visual disturbances, including vision blurred and diplopia |
| **Ear and labyrinth disorders**<br><br>Transient or permanent hearing loss |
| **Cardiac disorders**<br><br>Congestive heart failure |
| **Respiratory, thoracic and mediastinal disorders**<br><br>Dyspnoea |
| **Gastrointestinal disorders**<br><br>Pancreatitis |
| **Hepatobiliary disorders**<br><br>Serious hepatotoxicity (including cases of fatal acute liver failure) |
| **Skin and subcutaneous tissue disorders**<br><br>Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, alopecia, photosensitivity, acute generalised exanthematous pustulosis. |

| |
|---|
| **Investigations**<br>Increased blood creatinine phosphokinase (CPK) |

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

### 4.9 Overdose

In general, side effects reported with overdose have been consistent with those reported for itraconazole use (see section 4.8).

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

No specific antidote is available.

Itraconazole cannot be removed by haemodialysis.

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

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION

A 20.2.2 Antimicrobial (chemotherapeutic) medicines. Fungicides.

Itraconazole is a triazole antifungal medicine. *In vitro* studies demonstrate that itraconazole inhibits the growth of the following fungi pathogenic for humans, at concentrations usually ranging from ≤ 0,025 – 0,8 μg/ml: dermatophytes (*Trichophyton spp., Microsporum spp., Epidermophyton floccosum);* yeasts *(Cryptococcus neoformans, Candida spp.*); *Aspergillus spp., Histoplasma spp*., *Paracoccidioides brasiliensis; Sporothrix schenkii; Blastomyces dermatitidis; Pseudallescheria boydii*, *Penicillium marneffei*.

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

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*.

*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.

*In vitro* activity does not necessarily imply clinical efficacy.

## 5.2 Pharmacokinetic properties

*General pharmacokinetic characteristics*

Peak plasma concentrations are reached within 2,5 hours following administration of the oral solution.

The terminal half-life of itraconazole is about 40 hours after repeated dosing. The pharmacokinetics of itraconazole is characterized by non-linearity and, consequently, shows accumulation in plasma after multiple dose administration. Steady state concentrations are reached within 15 days, with $C_{max}$ values of about 2 µg/ml after oral administration of 200 mg once daily.

Itraconazole clearance decreases at higher doses due to a saturable mechanism of its hepatic metabolism. Itraconazole is excreted as inactive metabolites in the urine (~ 35 %) and in faeces (~ 54 %).

Itraconazole undergoes extensive hepatic metabolism to give numerous metabolites. The main metabolite is hydroxy-itraconazole, with plasma concentrations about twice those of the unchanged medicine. Similar to the parent, steady-state concentrations of hydroxy-itraconazole are reached approximately within 2 weeks of the first dose.

*Absorption*

The observed absolute bioavailability of itraconazole under fed conditions is about 55 % and is increased by 30 % when the oral solution is taken in fasting conditions.

*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 medicine. Itraconazole is distributed in a large apparent volume in the body (> 700 L): concentrations in lung, kidney, liver, bone, stomach, spleen and muscle at steady state were found to be two to three times higher than the corresponding trough concentrations in plasma. Brain to plasma ratios were

about 1. The uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma.

*Biotransformation*

Itraconazole is extensively metabolised by the liver into a large number of metabolites. The main metabolite is hydroxy-itraconazole, which has *in vitro* antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxy-metabolite are about twice those of itraconazole. As shown in *in-vitro* studies, CYP3A4 is the major enzyme that is involved in the metabolism of itraconazole.

*Excretion*

Itraconazole is excreted as inactive metabolites to about 35 % in urine within one week and to about 54 % with faeces. Renal excretion of the parent drug accounts for less than 0,03 % of the dose, whereas faecal excretion of unchanged itraconazole varies between 3 – 18% of the dose.

***SPECIAL POPULATIONS***

**Hepatic impairment**

Itraconazole is predominantly metabolised in the liver. A single oral dose (100 mg capsule) was administered to 12 patients with cirrhosis and six healthy control subjects: $C_{max}$, AUC and terminal half-life of itraconazole were measured, and compared between groups. Mean itraconazole $C_{max}$ was reduced significantly (by 47 %) in patients with cirrhosis. Mean elimination half-life was prolonged significantly compared to that found in subjects without hepatic impairment (37 vs. 16 hours, respectively). Overall exposure to itraconazole, based on AUC was significantly increased in cirrhotic patients and in healthy subjects. Data are not

available on efficacy and safety in cirrhotic patients during long-term use of itraconazole (see section 4.2 and section 4.4).

**Renal impairment**

Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when the medicine is administered in this patient population.

The elimination $t_{1/2}$ was increased from 18 to 24 hours. There are no safety data of repeated dosages under renal impairment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Inactive ingredients include the following: hypromellose, macrogol, and sugar spheres (composed of maize starch, purified water and sucrose).

The capsule itself is composed of erythrosine sodium, gelatin, indigotin disulphonate sodium and titanium dioxide.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store at or below 25 ºC in a dry place. Protect from light.

## 6.5 Nature and contents of container

Carton containing one or more blister strips of 4, 7 or 14 capsules each.

## 6.6 Special precautions for disposal and other handling

No special requirements.

# 7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty.) Ltd.

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# 8. REGISTRATION NUMBERS

TRISPORAL capsules: A39/20.2.2/0617

# 9 DATE OF FIRST AUTHORISATION

Date of registration:

TRISPORAL capsules: 06 October 2006

# 10 DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA:

To be advised