SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ITRANOL
Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains itraconazole 100 mg.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules for oral administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Itranol capsules are indicated for the treatment of the following conditions:

- **Vulvovaginal candidosis.**
- **Dermatomycosis.**
- **Oral Candidosis.**
- **Onychomycosis caused by dermatophytes and/or yeasts.**
- **Blastomycosis (pulmonary and extrapulmonary)**.
- **Histoplasmosis**.

4.2. Posology and method of administration

For optimal absorption, administer Itranol capsules immediately after a full meal.
The capsules must be swallowed whole.

Gynecological indication

Indication	Dose	Treatment Duration
Vulvovaginal candidosis	200 mg b.i.d. or 200 mg once daily	1 day or 3 days

Dermatological / mucosal / ophthalmological indications		
Indication	**Dose**	**Treatment Duration**
Dermatomycosis	200 mg once daily or 100 mg once daily	7 days or 15 days
Highly keratinized regions as in plantar tinea pedis and palmar tinea manus	200 mg b.i.d. or 100 mg once daily	7 days or 30 days
Pityriasis versicolor	200 mg once daily	7 days
Oral candidosis	100 mg once daily	15 days
In some immunocompromised patients (e.g. neutropenic, AIDS or organ transplant patients), the oral bioavailability of itraconazole from itraconazole capsules may be decreased. Therefore the doses may need doubling.		
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 b.i.d.) 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**
Aspergillosis	200 mg once daily	2-5 months	Increase dose to 200 mg b.i.d. in case of invasive or disseminated disease.

Candidosis	100 - 200 mg once daily	3 weeks - 7 months	Increase dose to 200 mg b.i.d. in case of invasive or disseminated disease.
Non-meningeal cryptococcosis	200 mg once daily	2 months - 1 year	
Cryptococcal meningitis	200 mg b.i.d.	2 months -1 year	Maintenance therapy: See section 4.4. *Special warnings and precautions for use.*
Histoplasmosis	200 mg once daily - 200 mg b.i.d.	8 months	
Blastomycosis	100 mg once daily -200 mg b.i.d.	6 months	
Lymphocutaneous and Cutaneous Sporotrichosis	100 mg once daily	3 months	
Paracoccidioido-mycosis	100 mg once daily	6 months	Data on the efficacy of itraconazole capsules at this dosage for treatment of paracoccidioido-mycosis in patients with AIDS is not available.
Chromomycosis	100 – 200 mg once daily	6 months	
[1] The duration of treatment should be adjusted depending on the clinical response.			

Special populations

Pediatrics

Clinical data on the use of itraconazole capsules in pediatric patients are limited. The use of Itranol capsules in pediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks. See section 4.4 *Special warnings and precautions for use.*

Elderly

Clinical data on the use of itraconazole capsules in elderly patients are limited. It is advised to use Itranol capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. See section 4.4 *Special warnings and precautions for use.*

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.

Hepatic impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. (See section 5.2 *Pharmacokinetic properties- Special populations, Hepatic impairment*).

4.3. Contraindications

- Itranol capsules are contraindicated in patients with hypersensitivity to the active substance (itraconazole) or to any of the excipients listed in section 6.1.
- Co-administration of a number of CYP3A4 substrates is contraindicated with Itranol capsules (see sections 4.4 and 4.5). These include:

Analgesics; Anaesthetics		
Ergot alkaloids (e.g. dihydroergotamine, ergometrine, ergotamine, methylergometrine)		
Anti-bacterials for Systemic Use; Anti-mycobacterials; Antimycotics for Systemic Use		
Isavuconazole		
Anthelmintics; Antiprotozoals		
Halofantrine		
Antihistamines for Systemic Use		
Astemizole	Mizolastine	Terfenadine
Antineoplastic Agents		
Irinotecan	Venetoclax (in patients with chronic lymphocytic leukaemia during dose initiation/titration/ramp-up phase of venetoclax)	
Antithrombotic Agents		
Dabigatran	Ticagrelor	
Antivirals for Systemic Use		
Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir)		

Cardiovascular System (Agents Acting on the Renin-Angiotensin System; Antihypertensives; Beta Blocking Agents; Calcium Channel Blockers; Cardiac Therapy; Diuretics)		
Aliskiren	Dronedarone	Nisoldipine
Bepridil	Eplerenone	Quinidine
Disopyramide	Ivabradine	Ranolazine
Dofetilide	Lercanidipine	Sildenafil (pulmonary hypertension)
Gastrointestinal Drugs, including Antidiarrheals, Intestinal Anti-inflammatory/Anti-infective Agents; Antiemetics and Antinauseants; Drugs for Constipation; Drugs for Functional Gastrointestinal Disorders		
Cisapride	Domperidone	Naloxegol
Lipid Modifying Agents		
Lovastatin	Lomitapide	Simvastatin
Psychoanaleptics; Psycholeptics (eg, antipsychotics, anxiolytics, and hypnotics)		
Lurasidone	Pimozide	Sertindole
Midazolam (oral)	Quetiapine	Triazolam
Urologicals		
Avanafil	Darifenacin	Solifenacin (in patients with severe renal impairment or moderate to severe hepatic impairment)
Dapoxetine	Fesoterodine (in patients with moderate or severe renal or hepatic impairment).	Vardenafil (in patients older than 75 years).
Miscellaneous Drugs and Other Substances		
Colchicine (in patients with renal or hepatic impairment)	Eliglustat (in patients that are CYP2D6 poor metabolisers (PM), CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) that are taking a strong or moderate CYP2D6 inhibitor).	

Increased plasma concentrations of these drugs, caused by coadministration with itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. 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 Section 4.5 *Interaction with other medicinal products and other forms of interaction*.

- Itranol 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 section 4.4 *Special warnings and precautions for use).*

- Itranol capsules must not be used during pregnancy except for life-threatening cases (See section 4.6 *Fertility, pregnancy and lactation*).

Women of childbearing potential taking Itranol capsules should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Itranol capsules therapy.

4.4. Special warnings and precautions for use

Cross-hypersensitivity

There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing Itranol capsules to patients with hypersensitivity to other azoles.

Cardiac effects

In a healthy volunteer study with itraconazole 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 itraconazole capsules has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.

Itranol should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g., total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other 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, Itranol should be discontinued.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be exercised when co-administering itraconazole and calcium channel blockers (see section 4.5 *Interaction with other medicinal products and other forms of interaction*) due to an increased risk of congestive heart failure.

Hepatic effects

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of itraconazole capsules. 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 Itranol capsules 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 metabolised 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 Itranol is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications.
(See section 5.2 *Pharmacokinetic properties- Special populations, Hepatic impairment*).

Reduced gastric acidity

Absorption of itraconazole from Itranol 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 Itranol 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 *Interaction with other medicinal products and other forms of interaction.*

Pediatrics

Clinical data on the use of itraconazole capsules in pediatric patients is limited. The use of Itranol 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 itraconazole capsules in elderly patients are limited. It is advised to use Itranol 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.

Hearing loss
Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see section 4.5 *Interaction with other medicinal products and other forms of interaction*). The hearing loss usually resolves when treatment is stopped but can persist in some patients.

Immunocompromised patients
In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), the oral bioavailability of Itranol capsules may be decreased. Impaired absorption in AIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. The dose should be adjusted based on the clinical response in these patients (see section 4.2). Therapeutic blood level monitoring may be necessary.

Patients with immediately life-threatening systemic fungal infections
Due to the pharmacokinetic properties (See section 5.2 *Pharmacokinetic properties*), Itranol capsules are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

Patients with AIDS
In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal or nonmeningeal) 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 plasma levels of itraconazole leading to subtherapeutic concentrations has been observed. The risk for subtherapeutic concentrations may be higher in < 16 year olds. If a patient does not respond to Itranol capsules, consideration should be given to switching to alternative therapy.

Neuropathy
If neuropathy occurs which may be attributable to Itranol capsules, the treatment should be discontinued.

Disorders of Carbohydrate Metabolism
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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 their sensitivity should be tested before the start of Itranol therapy.

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

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 section 4.3 *Contraindications* and section 4.5 *Interaction with other medicinal products and other forms of interaction*.

4.5. Interaction with other medicinal products and other forms of interaction

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Itraconazole is a strong CYP3A4 inhibitor and a P-glycoprotein inhibitor and Breast Cancer Resistance Protein (BCRP) inhibitor.
Itraconazole may modify the pharmacokinetics of other substances that share this metabolic or these protein transporter pathways.
Examples of drugs that may impact on the plasma concentration of itraconazole are presented by drug class in Table 1 below. Examples of drugs that may have their plasma concentrations impacted by itraconazole are presented in Table 2 below. Due to the number of interactions, the potential changes in safety or efficacy of the interacting drugs are not included. Please refer to the prescribing information of the interacting drug for more information.

The interactions described in these tables are categorised as contraindicated, not recommended or to be used with caution with itraconazole taking into account the extent of the concentration

increase and the safety profile of the interacting drug (see also sections 4.3 and 4.4 for further information). The interaction potential of the listed drugs was evaluated based on human pharmacokinetic studies with itraconazole, and/or human pharmacokinetic studies with other strong CYP3A4 inhibitors (e.g. ketoconazole) and/or in vitro data:

- 'Contraindicated': Under no circumstances is the drug to be co-administered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.
- 'Not recommended': The use of the drug should be avoided during and up to two weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If co-administration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the concomitantly administered drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations of the co administered drug be measured.
- 'Use with caution': Careful monitoring is recommended when the drug is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations of the co administered drug be measured.

The interactions listed in these tables have been characterised in studies that were performed with recommended doses of itraconazole. However, the extent of interaction may be dependent on the dose of itraconazole administered. A stronger interaction may occur at a higher dose or with a shorter dosing interval. Extrapolation of the findings with other dosing scenarios or different drugs should be done with caution.
Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors, the decline in plasma concentrations may be even more gradual. This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole. (See section 5.2)

Table 1: Examples of drugs that may impact the plasma concentration of itraconazole, presented by drug class

Examples of medicinal products (Per Orale [PO] Single Dose unless otherwise stated) within class	**Expected/Potential effect on itraconazole levels (↑ = increase; ↔ = no change; ↓ = decrease)**	**Clinical comment (see above for additional info and also sections 4.3 and 4.4)**
Antibacterials for Systemic Use; Antimycobacterials		

Isoniazid	Although not studied directly, isoniazid is likely to decrease the concentrations of itraconazole.	Not recommended
Rifampicin PO 600 mg OD	Itraconazole AUC ↓	Not recommended
Rifabutin PO 300 mg OD	Itraconazole C_{max} ↓ 71%, AUC ↓ 74%	Not recommended
Ciprofloxacin PO 500 mg BID	Itraconazole C_{max} ↑ 53%, AUC ↑ 82%	Use with caution
Erythromycin 1 g	Itraconazole C_{max} ↑ 44%, AUC ↑ 36%	Use with caution
Clarithromycin PO 500 mg BID	Itraconazole C_{max} ↑ 90%, AUC ↑ 92%	Use with caution
Antiepileptics		
Carbamazepine, Phenobarbital	Although not studied directly, these drugs are likely to decrease concentrations of itraconazole.	Not recommended
Phenytoin PO 300 mg OD	Itraconazole C_{max} ↓ 83%, AUC ↓ 93% Hydroxyitraconazole C_{max} ↓ 84%, AUC ↓ 95%	Not recommended
Antineoplastics Agents		
Idelalisib	Although not studied directly, idelalisib is likely to increase the concentrations of itraconazole.	Use with caution
Antivirals for Systemic Use		
Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir)	Although not studied directly, these drugs are expected to increase the concentrations of itraconazole.	Contraindicated
Efavirenz 600 mg	Itraconazole C_{max} ↓ 37%, AUC ↓ 39%; Hydroxyitraconazole C_{max} ↓ 35%, AUC ↓ 37%	Not recommended
Nevirapine PO 200 mg OD	Itraconazole C_{max} ↓ 38%, AUC↓62%	Not recommended
Cobicistat, Darunavir (boosted), Elvitegravir (ritonavir-boosted), Fosamprenavir (ritonavir- boosted), Ritonavir, Saquinavir (ritonavir-boosted)	Although not studied directly, these drugs are expected to increase the concentrations of itraconazole.	Use with caution

Indinavir PO 800 mg TID	Itraconazole concentration ↑	Use with caution
Calcium Channel Blockers		
Diltiazem	Although not studied directly, diltiazem is likely to increase the concentration of itraconazole.	Use with caution
Drugs for Acid Related Disorders		
Antacids (aluminum, calcium, magnesium, or sodium bicarbonate), H2-receptor antagonists (eg, cimetidine, ranitidine), Proton pump inhibitors (eg, lansoprazole, omeprazole, rabeprazole)	Itraconazole C_{max} ↓, AUC ↓	Use with caution
Respiratory System: Other Respiratory System Products		
Lumacaftor/Ivacaftor PO 200/250 mg BID	Itraconazole concentration ↓	Not recommended
Miscellaneous		
St. John's Wort *(Hypericum perforatum)*	Although not studied directly, St. John's Wort is likely to decrease the concentration of itraconazole.	Not recommended

Table 2 Examples of drugs that may have their plasma concentrations impacted by itraconazole, presented by drug class

Examples of medicinal products (PO Single Dose unless otherwise stated) within class	**Expected/Potential effect on drugs levels** **(↑ = increase; ↔ = no change; ↓ = decrease)**	**Clinical comment** **(see above for additional info and also sections 4.3 and 4.4)**
Analgesics; Anaesthetics		
Ergot alkaloids (eg, dihydroergotamine, ergometrine, ergotamine, methylergometrine)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Eletriptan, Fentanyl	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Alfentanil, Buprenorphine (IV and sublingual), Cannabinoids, Methadone, Sufentanil	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Oxycodone PO 10 mg,	Oxycodone PO: C_{max} ↑ 45%, AUC ↑ 2.4-fold	Use with caution
Oxycodone IV 0.1 mg/kg	Oxycodone IV: AUC ↑ 51%	Use with caution
Antibacterials for Systemic Use; Antimycobacterials; Antimycotics for Systemic Use		

Isavuconazole	Although not studied directly, itraconazole is likely to increase the concentrations of isavuconazole.	Contraindicated
Bedaquiline	Although not studied directly, itraconazole is likely to increase the concentrations of bedaquiline.	Not recommended
Rifabutin PO 300 mg OD	Rifabutin concentration ↑ (extent unknown)	Not recommended
Clarithromycin PO 500 mg BID	Clarithromycin concentration ↑	Use with caution
Delamanid	Although not studied directly, itraconazole is likely to increase the concentrations of delaminid.	Use with caution
Antiepileptics		
Carbamazepine	Although not studied directly, itraconazole is likely to increase the concentrations of carbamazepine.	Not recommended
Anti-inflammatory and Antirheumatic Products		
Meloxicam 15 mg	Meloxicam C_{max} ↓ 64%, AUC ↓ 37%	Use with caution
Anthelmintics; Antiprotozoals		
Halofantrine	Although not studied directly, itraconazole is likely to increase the concentrations of halofantrine.	Contraindicated
Artemether-lumefantrine, Praziquantel	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Quinine 300 mg	Quinine C_{max} ↔, AUC ↑ 96%	Use with caution
Antihistamines for Systemic Use		
Astemizole, Mizolastine, Terfenadine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Ebastine 20 mg	Ebastine C_{max} ↑ 2.5-fold, AUC ↑ 6.2-fold Carabastine C_{max}↔, AUC ↑ 3.1-fold	Not recommended
Bilastine, Rupatidine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution

Antineoplastic Agents		
Irinotecan	Although not studied directly, itraconazole is likely to increase the concentrations of irinotecan and its active metabolite.	Contraindicated
Mobocertinib	Mobocertinib Cmax ↑ ↑ ↑ 3.8-fold, AUC ↑ ↑ ↑ ↑ 8.4-fold	Contraindicated
Venetoclax	Although not studied directly, itraconazole is likely to increase the concentrations of venetoclax.	Contraindicated in patients with chronic lymphocytic leukaemia during dose initiation/titration/rampup phase of venetoclax. Otherwise, not recommended unless the benefits outweigh the risks. Refer to the venetoclax prescribing information.
Axitinib, Bosutinib, Cabazitaxel, Cabozantinib, Ceritinib, Crizotinib, Dabrafenib, Dasatinib, Docetaxel, Everolimus, Glasdegib, Ibrutinib, Lapatinib, Nilotinib, Pazopanib, Regorafenib, Sunitinib, Temsirolimus, Trabectedin, Trastuzumab emtansine, Vinca alkaloids (eg, vinflunine, vinorelbine)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs except for cabazitaxel and regorafenib. No statistically significant change in cabazitaxel exposure, but a high variability in the results was observed. Regorafenib AUC is expected to decrease (by estimation of active moiety)	Not recommended
Entrectinib	Entrectinib Cmax ↑ 73%, AUC ↑ 6.0 fold	Not recommended
Cobimetinib 10 mg,	Cobimetinib Cmax ↑ 3.2-fold, AUC ↑6.7-fold	Not recommended
Olaparib 100 mg	Olaparib Cmax ↑ 40%, AUC ↑ 2.7- fold	Not recommended
Talazoparib	Talazoparib Cmax ↑ 40%, AUC ↑ 56%	Not recommended
Alitretinoin (oral), Bortezomib, Brentuximab vedotin, Erlotinib, Idelalisib, Imatinib, Nintedanib, Panobinostat, Ponatinib, Ruxolitinib, Sonidegib, Tretinoin (Oral)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs	Use with caution
Pemigatinib	Pemigatinib Cmax ↑ 17%, AUC ↑ 91% ↑	Use with caution

Busulfan 1 mg/kg Q6h	Busulfan Cmax ↑, AUC ↑	Use with caution
Gefitinib 250 mg	Gefitinib 250 mg Cmax ↑, AUC ↑ 78%	Use with caution
Antithrombotic Agents		
Dabigatran, Ticagrelor	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Apixaban, Edoxaban, Rivaroxaban, Vorapaxar	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Cilostazol, Coumarins (eg, warfarin)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs	Use with caution
Antivirals for Systemic Use		
Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir)	Itraconazole may increase paritaprevir concentrations.	Contraindicated
Elbasvir/Grazoprevir, , Tenofovir alefenamide fumarate (TAF), Tenofovir disoproxil fumarate (TDF)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Cobicistat, Elvitegravir (ritonavir-boosted), Glecaprevir/Pibrentasvir, Maraviroc, Ritonavir, Saquinavir	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Indinavir PO 800 mg TID	Indinavir C_{max} ↔, AUC ↑	Use with caution
Cardiovascular System (Agents Acting on the Renin-Angiotensin System; Antihypertensives; Beta Blocking Agents; Calcium Channel Blockers; Cardiac Therapy; Diuretics)		
Bepridil, Disopyramide, Dofetilide, Dronedarone, Eplerenone, Ivabradine, Lercanidipine, Nisoldipine, Ranolazine, Sildenafil (pulmonary hypertension)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Finerenone	Although not studied directly, itraconazole is likely to increase the concentrations of these	Contraindicated
Aliskiren 150 mg,	Aliskiren C_{max} ↑ 5.8-fold, AUC ↑ 6.5-fold	Contraindicated
Quinidine 100 mg	Quinidine C_{max} ↑ 59%, AUC ↑ 2.4- fold	Contraindicated
Felodipine 5 mg	Felodipine C_{max} ↑ 7.8-fold, AUC ↑ 6.3-fold	Not recommended
Riociguat, Tadalafil (pulmonary hypertension)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended

Bosentan, Diltiazem, Guanafacine, Other Dihydropyridines (eg, amlodipine, isradipine, nifedipine, nimodipine), Verapamil	Although not studied directly, itraconazole is likely to increase the concentrations of bosentan.	Use with caution
Digoxin 0.5 mg	Digoxin C_{max} ↑ 34%, AUC ↑68%	Use with caution
Nadolol 30 mg	Nadolol C_{max} ↑ 4.7-fold, AUC ↑ 2.2-fold	Use with caution
Corticosteroids for Systemic Use; Drugs for Obstructive Airway Diseases		
Ciclesonide, Salmeterol	Although not studied directly, itraconazole is likely to increase the concentrations of salmeterol and the active metabolite of ciclesonide.	Not recommended
Budesonide INH 1 mg SD,	Budesonide INH C_{max} ↑ 65%, AUC ↑ 4.2-fold; Budesonide (other formulations) concentration ↑	Use with caution
Dexamethasone IV 5 mg Dexamethasone PO 4.5 mg	Dexamethasone IV: C_{max} ↔, AUC ↑ 3.3-fold Dexamethasone PO: C_{max} ↑ 69%, AUC ↑ 3.7-fold	Use with caution
Fluticasone INH 1 mg BID,	Fluticasone INH concentration ↑	Use with caution
Methylprednisolone 16 mg,	Methylprednisolone PO C_{max} ↑ 92%, AUC ↑ 3.9-fold Methylprednisolone IV AUC ↑ 2.6-fold	Use with caution
Fluticasone nasal	Although not studied directly, itraconazole is likely to increase the concentrations of nasally- administered fluticasone.	Use with caution
Drugs Used in Diabetes		
Repaglinide 0.25 mg	Repaglinide C_{max} ↑ 47%, AUC ↑ 41%	Use with caution
Saxagliptin	Although not studied directly, itraconazole is likely to increase the concentrations of saxagliptin.	Use with caution
Gastrointestinal Drugs, including Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents; Antiemetics and Antinauseants; Drugs for Constipation; Drugs for Functional Gastrointestinal Disorders		
Cisapride, Naloxegol	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated

Domperidone 20 mg	Domperidone C_{max} ↑ 2.7-fold, AUC ↑ 3.2-fold	Contraindicated
Aprepitant, Loperamide, Netupitant	Although not studied directly, itraconazole is likely to increase the concentrations of aprepitant.	Use with caution
Immunosuppressants		
Sirolimus (rapamycin)	Although not studied directly, itraconazole is likely to increase the concentrations of sirolimus.	Not recommended
Cyclosporine, Tacrolimus	Although not studied directly, itraconazole is likely to increase the concentrations of cyclosporine.	Use with caution
Tacrolimus IV 0.03 mg/kg OD	Tacrolimus IV concentration ↑	Use with caution
Voclosporin	Although not studied directly, itraconazole is	Contraindicated
Lipid Modifying Agents		
Lomitapide	Although not studied directly, itraconazole is likely to increase the concentrations of lomitapide.	Contraindicated
Lovastatin 40 mg,	Lovastatin C_{max} ↑ 14.5->20-fold, AUC ↑ >14.8 - >20-fold Lovastatin acid C_{max} ↑ 11.5-13- fold, AUC ↑ 15.4-20-fold	Contraindicated
Simvastatin 40 mg	Simvastatin acid C_{max} ↑ 17-fold, AUC ↑ 19-fold	Contraindicated
Atorvastatin	Atorvastatin acid: C_{max} ↔ to ↑2.5 fold, AUC ↑ 40% to 3-fold	Not recommended
Psychoanaleptics; Psycholeptics (eg, antipsychotics, anxiolytics, and hypnotics)		
Lurasidone, Pimozide, Quetiapine, Sertindole	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Midazolam (oral) 7.5 mg	Midazolam (oral) C_{max} ↑ 2.5 to 3.4-fold, AUC ↑ 6.6 to 10.8-fold	Contraindicated
Triazolam 0.25 mg	Triazolam C_{max} ↑, AUC ↑	Contraindicated
Alprazolam 0.8 mg	Alprazolam C_{max} ↔, AUC ↑ 2.8- fold	Use with caution

Aripiprazole 3 mg	Aripiprazole C_{max} ↑ 19%, AUC ↑ 48%	Use with caution
Brotizolam 0.5 mg	Brotizolam C_{max} ↔, AUC ↑ 2.6-fold	Use with caution
Buspirone 10 mg	Buspirone C_{max} ↑ 13.4-fold, AUC ↑ 19.2-fold	Use with caution
Midazolam (iv) 7.5 mg	Midazolam (iv) 7.5 mg: concentration ↑; Although not studied directly, itraconazole is likely to increase the concentrations of midazolam following oromucosal administration.	Use with caution
Risperidone 2-8 mg/day	Risperidone and active metabolite concentration ↑	Use with caution
Zopiclone 7.5 mg	Zopiclone C_{max} ↑ 30%, AUC ↑ 70%	Use with caution
Cariprazine, Galantamine, Haloperidol, Reboxetine, Venlafaxine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Respiratory System: Other Respiratory System Products		
Lumacaftor/Ivacaftor PO 200/250 mg BID	Ivacaftor C_{max} ↑ 3.6-fold, AUC ↑ 4.3-fold Lumacaftor C_{max} ↔, AUC↔	Not recommended
Ivacaftor	Although not studied directly, itraconazole is likely to increase the concentrations of ivacaftor.	Use with caution
Sex Hormones and Modulators of the Genital System; Other Gynecologicals		
Cabergoline, Dienogest, Ulipristal	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Urologicals		
Avanafil, Dapoxetine, Darifenacin	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated

Fesoterodine	Although not studied directly, itraconazole is likely to increase the concentrations of the active metabolites, 5-hydroxymethyl- tolterodine.	Moderate or severe renal or hepatic impairment: Contraindicated Mild renal or hepatic impairment: Concomitant use should be avoided Normal renal or hepatic impairment: Use with caution with a maximum fesoterodine dose of 4 mg.
Solifenacin	Although not studied directly, itraconazole is likely to increase the concentrations of solifenacin.	Severe renal impairment: Contraindicated Moderate or severe hepatic impairment: Contraindicated Use with caution in all other patients with a maximum solifenacin dose of 5 mg.
Vardenafil	Although not studied directly, itraconazole is likely to increase the concentrations of vardenafil.	Contraindicated in patients older than 75 years; otherwise not recommended.
Alfuzosin, Silodosin, Tadalafil (erectile dysfunction and benign prostatic hyperplasia), Tamsulosin, Tolterodine	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Dutasteride, Imidafenacin, Sildenafil (erectile dysfunction)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Use with caution
Oxybutynin 5 mg	Oxybutynin C_{max} ↑ 2-fold, AUC ↑ 2-fold N-desethyloxybutynin C_{max} ↔, AUC↔ Following transdermal administration: Although not studied directly, itraconazole is likely to increase the concentrations of oxybutynin following transdermal administration.	Use with caution
Miscellaneous Drugs and Other Substances		

Valbenazine	Valbenazine Cmax (↑), AUC (↑ ↑)	Use with caution, monitor for valbenazine-related adverse reactions, dose reduction of valbenazine is necessary.
Colchicine	Although not studied directly, itraconazole is likely to increase the concentrations of colchicine	Contraindicated in patients with renal or hepatic impairment. Not recommended in other patients.
Eliglustat	Although not directly studied, itraconazole is expected to increase the concentrations of eliglustat.	Contraindicated in CYP2D6 poor metabolisers (PM). Contraindicated in CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) taking a strong or moderate CYP2D6 inibitor. Use with caution in CYP2D6 IMs and EMs. In CYP2D6 EMs with mild hepatic impairment, an eliglustat dose of 84 mg/day should be considered.
Cinacalcet	Although not studied directly, itraconazole is likely to increase the concentrations of cinacalcet.	Use with caution

4.6. Fertility, pregnancy and lactation

Pregnancy
Itranol Capsules 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 section 4.3).

In animal studies itraconazole has shown reproduction toxicity (See section 5.3).

There is limited information on the use of itraconazole during pregnancy. During post-marketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations. A causal relationship with itraconazole has not been established.

Epidemiological data on exposure to itraconazole 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 Itranol capsules should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Itranol therapy.

Lactation
A very small amount of itraconazole is excreted in human milk. The expected benefits of Itranol therapy should be weighed against the risks of breast-feeding. In case of doubt, the patient should not breast-feed.

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 itraconazole 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 subsection *Tabulated list of adverse reactions* 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.

Tabulated list of adverse reactions

The ADRs in the table below were derived from open-label and double-blind clinical trials with Itranol Capsules involving 8499 patients in the treatment of dermatomycoses or onychomycosis, and from spontaneous reporting.

The table below presents ADRs by System Organ Class. Within each System Organ Class, the ADRs are presented by incidence, using the following convention:

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).

Adverse Drug Reactions	
Infections and infestations	
Uncommon	Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and lymphatic system disorders	
Rare	Leukopenia
Immune system disorders	
Uncommon	Hypersensitivity*
Rare	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Endocrine disorders	
Not known	Pseudoaldosteronism
Metabolism and nutrition disorders	
Rare	Hypertriglyceridaemia
Nervous system disorders	
Common	Headache
Rare	Tremor, Paraesthesia, Hypoaesthesia, Dysgeusia
Eye disorders	
Rare	Visual disturbance (including diplopia and blurred vision)
Ear and labyrinth disorder	
Rare	Transient or permanent hearing loss*, Tinnitus
Cardiac disorders	
Rare	Congestive heart failure*
Respiratory, thoracic and mediastinal disorders	
Rare	Dyspnoea
Gastrointestinal disorders	

Adverse Drug Reactions	
Common	Abdominal pain, Nausea
Uncommon	Diarrhoea, Vomiting, Constipation, Dyspepsia, Flatulence
Rare	Pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic function abnormal
Rare	Serious hepatotoxicity (including some cases of fatal acute liver failure)*, Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, Rash, Pruritus
Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Renal and urinary disorders	
Rare	Pollakiuria
Reproductive system and breast disorders	
Uncommon	Menstrual disorder
Rare	Erectile dysfunction
General disorders and administration site conditions	
Rare	Oedema
Investigations	
Rare	Blood creatine phosphokinase increased

see section 4.4

Description of selected adverse reactions

The following is a list of ADRs associated with itraconazole that have been reported in clinical trials of itraconazole oral Solution and itraconazole I.V., excluding the ADR 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: 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: 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

Pediatric population

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

Based on pooled safety data from these clinical trials, the commonly reported adverse drug reactions (ADRs) in pediatric patients were Headache (3.0%), Vomiting (3.0%), Abdominal pain (2.4%), Diarrhoea (2.4%), Hepatic function abnormal (1.2%), Hypotension (1.2%), Nausea (1.2%), and Urticaria (1.2%). In general, the nature of ADRs in pediatric patients is similar to that observed in adult subjects, but the incidence is higher in the pediatric patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9. Overdose

Symptoms and signs
In general, adverse events reported with overdose have been consistent with those reported for itraconazole use. (See section 4.8 *Undesirable effects*).

Treatment
In the event of overdosage, supportive measures should be employed. Itraconazole cannot be removed by hemodialysis. No specific antidote is available.
It is advisable to contact a poison control centre to determine the latest recommendations for the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic classification

Antimycotics for systemic use, triazole derivatives

ATC code: J02A C02
Itraconazole, a triazole derivative, has a broad spectrum of activity.

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.

Using CLSI methods, interpretive breakpoints for itraconazole have not been established for Candida species and filamentous fungi.

For itraconazole, breakpoints have only been established by CLSI for *Candida* spp. from superficial mycotic infections (CLSI M27-A2). The CLSI breakpoints are as follows: susceptible ≤0.125; susceptible, dose- dependent 0.25-0.5 and resistant ≥1 µg/mL. Interpretive breakpoints have not been established for the filamentous fungi.

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

EUCAST breakpoints have yet to be established for itraconazole and Candida spp.

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

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

Candida krusei, Candida glabrata and *Candida guillermondii* are generally the least susceptible. *Candida* species, with some 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 proliferans* and *Scopulariopsis spp*.

Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14α-demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux. Cross-resistance between

members of the azole class has been observed within *Candida* spp., although resistance to one member of the class does not necessarily confer resistance to other azoles. Itraconazole-resistant strains of *Aspergillus fumigatus* have been reported.

5.2. Pharmacokinetic properties

General pharmacokinetic characteristics

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with C_{max} values of 0.5 µg/ml, 1.1 µg/ml and 2.0 µg/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

Absorption

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral capsule dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H_2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see section 4.4 *Special Warnings and Precautions for use*, and section 4.5 *Interactions*). Absorption of itraconazole under fasted conditions in these subjects is increased when itraconazole capsules are administered with an acidic beverage (such as a non-diet cola). When itraconazole capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H_2-receptor antagonist, itraconazole absorption was comparable to that observed when itraconazole capsules were administered alone. (See section 4.5 *Interactions*.)

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given. (See section 4.4 *Special Warnings and Precautions for use*.)

Distribution

Most of the itraconazole in plasma is bound to protein (99.8%) with albumin being the main binding component (99.6% for the hydroxy-metabolite). It has also a marked affinity for

lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (> 700L), suggesting its extensive distribution into tissues: Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma, and the uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

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

Excretion
Itraconazole is excreted mainly as inactive metabolites in urine (35%) and feces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, fecal excretion of unchanged drug varies between 3 - 18% of the dose.

Special Populations

Hepatic impairment:
Itraconazole is predominantly metabolised in the liver. A pharmacokinetic study using a single 100 mg dose of itraconazole (one 100 mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. A statistically significant reduction in average C_{max} (47%) and a two fold increase in the elimination half-life (37 ± 17 versus 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC, was similar in cirrhotic patients and in healthy subjects.

Data are not available in cirrhotic patients during long-term use of itraconazole. (See section 4.2 *Posology and method of administration*, and section 4.4 *Special warnings and precautions for use*.)

Renal impairment:
Limited data are available on the use of oral itraconazole in patients with renal impairment.

A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 ml/min. × 1.73 m^2, the exposure, based on AUC, was slightly reduced compared

with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max}, C_{max}, and AUC_{0-8h}). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50-79 ml/min), moderate (defined in this study as CrCl 20-49 ml/min), and severe renal impairment (defined in this study as CrCl <20 ml/min) were similar to that in healthy subjects, (range of means 42-49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively.) Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole. (See also section 4.2 *Posology and method of administration, and* section 4.4 *Special warnings and precautions for use.)*

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

5.3. Preclinical safety data

Itraconazole

Acute oral toxicity studies with itraconazole in mice, rats, guinea-pigs and dogs indicate a wide safety margin (3- to 16 fold of Maximum Recommended Human Dose [MRHD] of 400 mg/day based on mg/m^2/day).

Itraconazole is not a primary carcinogen in rats to 13 mg/kg/day (males) and 52 mg/kg/day (females), or mice up to 80 mg/kg/day (1-fold of MRHD based on mg/m^2/day).

Nonclinical data on itraconazole revealed no indications for gene toxicity, primary carcinogenicity or impairment of fertility. At high doses, of 40 and 80 mg/kg/day in rats (1- and 2-fold of MRHD based on mg/m^2/day), effects were observed in the adrenal cortex, liver and the mononuclear phagocyte system but appear to have a low relevance for the proposed clinical use. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats and mice at high doses. A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, (no toxicity was observed up to 20 mg/kg/day (2-fold of MRHD based on mg/m^2/day), and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

Reproductive toxicology
Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at 40 and 160 mg/kg/day (1- and 4-fold of MRHD based on mg/m^2/day) and mice at 80 and 160 mg/kg/day (1, 2 and 28 fold of MRHD based on mg/m2/day). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and macroglossia. No teratogenic effects were found in rabbits up to 80 mg/kg/day dose (4-fold of MRHD based on mg/m^2/day).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose, hypromellose, gelatin, maize (corn) starch, poloxamer 188, titanium dioxide, quinoline yellow (E-104), indigo carmine (E-132), purified water, Anhydrous Ethanol, Methylen Chloride

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 25° C in the original package.

Keep out of reach of children.

6.5. Nature and contents of container

14 green capsules in blister packs.

6.6. Special precautions for disposal and other handling

No special requirements.

7. REGISTRATION HOLDER:

Rafa Laboratories Ltd, POB 405, Jerusalem 9100301
Registration No: 132-86-31044

8. MANUFACTURER:

Laboratorios Liconsa S.A, Barcelona Spain.

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