1. NAME OF THE MEDICINAL PRODUCT

ITRANOL
Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg itraconazole.

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 notavailable.
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. 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 who have received treatment for a systemic fungal infection with itraconazol capsules and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

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.

Quinoline yellow (E-104)
The capsules **contain** quinoline yellow (E-104) which may cause allergic reactions.

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 4.5 *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 metabolised through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Similarly, itraconazole may modify the pharmacokinetics of other substances that share this metabolic pathway. Itraconazole is a potent CYP3A4 inhibitor and a P-glycoprotein inhibitor. When using concomitant medication, it is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust dosages.

Drugs that may decrease itraconazole plasma concentrations

Drugs that reduce the gastric acidity (e.g. acid neutralising medicines such as aluminum hydroxide, or acid secretion suppressors such as H2-receptor antagonists and proton pump inhibitors) impair the absorption of itraconazole from itraconazole capsules. It is recommended that these drugs be used with caution when coadministered with itraconazole capsules:

> It is recommended that itraconazole be administered with an acidic beverage (such as non-diet cola) upon co-treatment with drugs reducing gastric acidity.
>
> It is recommended that acid neutralising medicines (e.g. aluminum hydroxide) be administered at least 1 hour before or 2 hours after the intake of Itranol capsules.
>
> Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Coadministration of itraconazole with potent enzyme inducers of CYP3A4 may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be largely reduced. Examples include:

Antibacterials: isoniazid, rifabutin (see also under *Drugs that may have their plasma concentrations increased by itraconazole)*, rifampicin.

Anticonvulsants: carbamazepine, (see also under *Drugs that may have their plasma concentrations increased by itraconazole*), phenobarbital, phenytoin.

Antivirals: efavirenz, nevirapine.

Therefore, administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these drugs be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon coadministration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Drugs that may increase itraconazole plasma concentrations

Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole. Examples include:

Antibacterials: ciprofloxacin, clarithromycin, erythromycin,

Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir (see also under *Drugs that may have their plasma concentrations increased by itraconazole*), ritonavir (see also *under Drugs that may have their plasma concentrations increased by itraconazole*),

It is recommended that these drugs be used with caution when coadministered with itraconazole capsules. It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured.

Drugs that may have their plasma concentrations increased by itraconazole

Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of drugs metabolised by CYP3A4 and can inhibit the drug transport by P-glycoprotein, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. CYP3A4-metabolised drugs known to prolong the QT interval may be contraindicated with itraconazole, since the combination may lead to ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. 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.

The interacting drugs are categorized as follows:

- 'Contraindicated': Under no circumstances is the drug to be coadministered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.
- 'Not recommended': It is recommended that the use of the drug 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 coadministration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations 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 be measured.

Examples of drugs that may have their plasma concentrations increased by itraconazole presented by drug class with advice regarding coadministration with itraconazole:

Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**
Alpha Blockers		tamsulosin	
Analgesics	levacetylmethadol (levomethadyl), methadone	fentanyl	alfentanil, buprenorphine IV and sublingual, oxycodone
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin
Antibacterials		rifabutin[a]	
Anticoagulants and Antiplatelet Drugs		rivaroxaban	coumarins, cilostazol, dabigatran

Drug Class	Contraindicated	Not Recommended	Use with Caution
Anticonvulsants		carbamazepine[a]	
Antidiabetics			repaglinide, saxagliptin
Antihelmintics and Antiprotozoals	halofantrine		praziquantel
Antihistamines	astemizole, mizolastine, terfenadine		ebastine
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)		eletriptan
Antineoplastics	irinotecan	dasatinib, nilotinib, trabectedin	bortezomib, busulphan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids

Drug Class	Contraindicated	Not Recommended	Use with Caution
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, oral midazolam, pimozide, sertindole, triazolam		alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone
Antivirals			maraviroc, indinavir[b], ritonavir[b], saquinavir
Beta Blockers			nadolol
Calcium Channel Blockers	bepridil, felodipine, lercanidipine, nisoldipine		other dihydropyridines, including verapamil
Cardiovascular Drugs, Miscellaneous	ivabradine, ranolazine	aliskiren	
Diuretics	eplerenone		
Gastrointestinal Drugs	cisapride,		aprepitant,

Drug Class	Contraindicated	Not Recommended	Use with Caution
			domperidone
Immunosuppressants		everolimus	budesonide, ciclesonide, ciclosporin, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus
Lipid Regulating Drugs	lovastatin, simvastatin		atorvastatin
Respiratory Drugs		salmeterol	
SSRIs, Tricyclics and Related Antidepressants			reboxetine
Urological Drugs		vardenafil	fesoterodine. imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine
Other	colchicine, in subjects with renal or hepatic	Colchicine,	alitretinoin (oral formulation),

Drug Class	Contraindicated	Not Recommended	Use with Caution
	impairment		cinacalcet, mozavaptan, tolvaptan

[a]See also under *Drugs that may decrease itraconazole plasma concentrations*

[b] See also under *Drugs that may increase itraconazole plasma concentrations*

Drugs that may have their plasma concentrations decreased by itraconazole

Coadministration of itraconazole with the NSAID meloxicam may decrease the plasma concentrations of meloxicam. It is recommended that meloxicam be used with caution when co-administered with itraconazole, and its effects or side effects be monitored. It is recommended that the dosage of meloxicam, if coadministered with itraconazole, be adapted if necessary.

Pediatric Population

Interaction studies have only been performed in adults.

4.6. Fertility, pregnancyand 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.

Women of childbearing potential

Women of childbearing potential taking Itranol capsules should use contraceptive precautions. Effective contraception should be continued until the next 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
Metabolism and nutrition disorders	
Rare	Hypertriglyceridaemia
Nervous system disorders	
Common	Headache
Rare	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	
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, Tremor

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

Paediatric population

The safety of itraconazole capsules was evaluated in 165 paediatric 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 paediatric 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 paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric 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. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by hemodialysis. No specific antidote is available.

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.

For itraconazole, breakpoints have only been established for *Candida* spp. from superficial mycotic infections (CLSI M27-A2, breakpoints have not been established for EUCAST

methodology). 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.

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:

dermatophytes *(Trichophyton spp., Microsporum spp., Epidermophyton floccosum*); yeasts *(Candida spp*., including *C. albicans, C. tropicalis, C. parapsilosis* and *C. krusei, Cryptococcus neoformans, Malassezia spp., Trichosporon spp., Geotrichum spp.); Aspergillus spp.; Histoplasma spp.*, including *H. capsulatum; Paracoccidioides brasiliensis; Sporothrix schenckii; Fonsecaea spp.; Cladosporium spp.; Blastomyces dermatitidis; Coccidiodes immitis; Pseudallescheria boydii; Penicillium marneffei;* and various other yeasts and fungi.

Candida krusei, *Candida glabrata* and *Candida tropicalis* 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 radiolabeled 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

Nonclinical data on itraconazole revealed no indications for gene toxicity, primary carcinogenicity or impairment of fertility. At high doses, 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, and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose, hypromellose, gelatin, poloxamer 188, maize (corn) starch, titanium dioxide, quinoline yellow (E-104), indigo carmine (E-132).

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.

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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