SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eszol 100mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Itraconazole BP…… 100 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.
Description: Pink, capsule shaped film coated tablets, 'ITR 100' embossed on one side of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mycoses, caused by pathogenic agents sensitive to itraconazole: vulvovaginal candidomycosis; dermatological/ophtalmological fungal diseases: dermatomicosis, pityriasis versicolor, fungal keratitis, oral moniliasis; onychomycosis, caused by dermatophytes and/or yeasts; systemic mycosis: systemic aspergillosis, cryptococcosis (including cryptococcal meningitis): to patients with depressed immune system and to all patients with cryptococcosis of CNS Eszol is administered only in case of ineffective treatment by other antifungal agents; histoplasmosis, sporotrichosis, paracoccidioidosis, blastomycosis and other systemic mycosis, which occur very rarely, and tropical mycosis.

4.2 Posology and method of administration

Eszol is for oral administration and should be taken immediately after a meal for maximal absorption. The tablets must be swallowed whole.
Tablets should be swallowed without chewing.
Treatment schedules in adults for each indication are as follows:

Indication	***Dose***	***Remarks***
Vulvovaginal candidosis	200 mg twice daily for 1 day	--
Pityriasis versicolor	200 mg once daily for 7 days	--
Tinea corporis, tinea cruris	100 mg once daily for 15 days or 200 mg once daily for 7 days	--
Tinea pedis, tinea manuum	100 mg once daily for 30 days	--

Oropharyngeal candidosis	100 mg once daily for 15 days	Increase dose to 200 mg once daily for 15 days in AIDS or neutropenic patients because of impaired absorption in these groups.
Onychomycosis (toenails with or without fingernail involvement)	200 mg once daily for 3 months	--

For skin, vulvovaginal and oropharyngeal infections, optimal clinical and mycological effects are reached 1 - 4 weeks after cessation of treatment and for nail infections, 6 - 9 months after the cessation of treatment. This is because elimination of itraconazole from skin, nails and mucous membranes is slower than from plasma.
The length of treatment for systemic fungal infections should be dictated by the mycological and clinical response to therapy:

Indication	***Dose[1]***	***Remarks***
Aspergillosis	200 mg once daily	Increase dose to 200 mg twice daily in case of invasive or disseminated disease
Candidosis	100-200 mg once daily	Increase dose to 200 mg twice daily in case of invasive or disseminated disease
Non-meningeal Cryptococcosis	200 mg once daily	
Cryptococcal meningitis	200 mg twice daily	See Special warnings and special precautions for use.
Histoplasmosis	200 mg once daily - 200 mg twice daily	---
Maintenance in AIDS	200 mg once daily	See absorption
Prophylaxis in neutropenia	200 mg once daily	See absorption

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

Impaired absorption in AIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. In such cases, blood level monitoring and if necessary, an increase in itraconazole dose to 200 mg twice daily, is indicated.

Special populations

Paediatrics

Clinical data on the use of Eszol tablets in paediatric patients are limited. The use of Eszol tablets in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.

Elderly

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.

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.

4.3 Contraindications

Hypersensitivity to itraconazole.
Coadministration of a number of CYP3A4 substrates is contraindicated with Eszol tablets. 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 Interaction with other medicinal products and other forms of interaction.

Eszol Tablets 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 in Special warnings and precautions for use).

Eszol Tablets must not be used during pregnancy except for life-threatening cases (see pregnancy and lactation)

Women of childbearing potential taking Eszol Tablets should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Eszol Tablets 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 Eszol Tablets to patients with hypersensitivity to other azoles.

Cardiac effects
Itraconazole has been shown to have a negative inotropic effect and Eszol Tablets 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.

Eszol Tablets 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, Itraconazole 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 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 Tablets. 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 Eszol Tablets 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 tablets 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 Itraconazole is strongly discouraged unless there is a serious or life-threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. (See Pharmacokinetic properties - Special Populations, Hepatic impairment.)

Reduced gastric acidity
Absorption of itraconazole from Eszol Tablets 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 Eszol Tablets with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary. See Interaction with other medicinal products and other forms of interaction.

Paediatrics
Clinical data on the use of Eszol Tablets in paediatric patients is limited. The use of Eszol Tablets in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.

Elderly
Clinical data on the use of Eszol Tablets in elderly patients are limited. It is advised to use Eszol Tablets 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 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 Eszol Tablets may be decreased.

Patients with immediately life-threatening systemic fungal infections
Due to the pharmacokinetic properties (See Pharmacokinetic properties), Eszol Tablets 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 non-meningeal) 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 Eszol Tablets, 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 Itraconazole therapy.

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 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 Eszol tablets. It is recommended that these drugs be used with caution when coadministered with Eszol tablets:
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 Eszol Tablets.
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 Eszol tablets. 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 co-administration 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 co-administered with itraconazole. Upon co-administration, 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.

Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**
Alpha Blockers		Tamsulosin	
Analgesics	levacetylmethadol (levomethadyl), methadone	Fentanyl	alfentanil, buprenorphine IV and sublingual,
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin
Antibacterials		Rifabutin[a]	
Anticoagulants and Antiplatelet		Rivaroxaban	coumarins, cilostazol, dabigatran
Anticonvulsants		Carbamazepine[a]	
Antidiabetics			repaglinide ,
Antihelmintics and	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
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, 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			Reboxetine
Urological Drugs		Vardenafil	fesoterodine. imidafenacin, sildenafil, solifenacin, tadalafil,
Other	colchicine, in subjects with renal or hepatic impairment	Colchicine	alitretinoin (oral formulation), cinacalcet, mozavaptan,
a See also under *Drugs that may decrease itraconazole plasma concentrations* b See also under *Drugs that may increase itraconazole plasma concentrations*			

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

Drugs that may have their plasma concentrations decreased by itraconazole
Co-administration 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 co-administered with itraconazole, be adapted if necessary.

Paediatric Population
Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation

Pregnancy
Eszol Tablets must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see Contraindications).
In animal studies itraconazole has shown reproduction toxicity (see Preclinical safety data). 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 child bearing potential
Women of childbearing potential taking itraconazole tablets should use contraceptive precautions. Effective contraception should be continued until the next menstrual period following the end of Itraconazole therapy.
Lactation
A very small amount of itraconazole is excreted in human milk. The expected benefits of Itraconazole 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 Undesirable effects), which may occur in some instances, must be taken into account.

4.8 Undesirable effects

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,
Renal and urinary disorders	
Rare	Pollakiuria
Reproductive system and breast disorders	
Uncommon	Menstrual disorder
Rare	Erectile dysfunction
General	
Rare	Oedema
Investigations	
Rare	Blood creatine phosphokinase increased

**see Special warnings and precautions for use*

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. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Symptoms and signs
In general, adverse events reported with overdose have been consistent with those reported for itraconazole use. (See 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 haemodialysis. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antifungal agents for systemic use.
ATC Code: J02A C02.

5.1 Pharmacodynamics

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 ≥ 1μg/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 Pharmacokinetics

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 Cmax 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 dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the tablets are taken immediately after a full meal.
Absorption of Eszol tablets is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see Special Warnings and Precautions for use, and Interactions). Absorption of itraconazole under fasted conditions in these subjects is increased when Eszol tablets are administered with an acidic beverage (such as a non-diet cola). When Eszol tablets were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H2-receptor antagonist, itraconazole absorption was comparable to that observed when Eszol tablets were administered alone. (See Interactions with other medicinal products and other forms of

interaction)
Itraconazole exposure is lower with the tablets formulation than with the oral solution when the same dose of drug is given. (See 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 (> 700 L), 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 faeces (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, faecal excretion of unchanged drug varies between 3 – 18% of the dose.

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
Sugar pellets, Hydroxypropyl methyl cellulose, Isopropyl alcohol, Dichloromethane, Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Povidone K-30, L-Hydroxypropyl cellulose, Sodium starch glycolate (type A), Colloidal silicon dioxide, Magnesium stearate, Opadry II pink 85 G 54039 and Purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.
Keep all medicines out of reach of children.

6.5 Nature and contents of container

10 tablets per blister. 1, 3 or 10 such blisters are packed in a carton along with packaging insert.

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

Kusum Healthcare Pvt. Ltd.
SP-289(A), RIICO Industrial Area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan) India

8. MARKETING AUTHORISATION NUMBER(S)

07726/08419/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 August 2022

10. DATE OF REVISION OF THE TEXT

08/2023

11. REFERENCES

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