

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Itraconazol Actavis 100 mg, hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 capsule contains: Itraconazole 100 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Opaque blue gelatin capsules containing a yellowish powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Itraconazole is indicated for the treatment of the following fungal infections verified by direct microscopy and /or cultures where systemic treatment is considered necessary:

Vulvovaginal candidiasis, Oral candidiasis, Pityriasis versicolor, Dermatomycoses, Onychomycoses (caused by dermatophytes and yeasts).

Consideration should be given to the official guidelines on the appropriate use of antifungal agents.

4.2 Posology and method of administration

Itraconazol Actavis capsules are for oral use

The capsules should be taken immediately after meals

The capsules should be swallowed whole.

Adults:

Vulvovaginal candidiasis.

200 mg in the morning and 200 mg in the evening for 1 day.

Oral candidiasis:

100 mg once daily for 2 weeks.

Pityriasis versicolor:

200 mg once daily for 1 week.

Tinea corporis/cruris:
100 mg once daily for 2 weeks.

Tinea pedis/manus:
100 mg twice daily for 4 weeks.

Onychomycoses:

Pulse treatment:

Toenail infection with or without fingernail infection:

200 mg twice daily for 7 days, followed by a treatment-free interval of 3 weeks, for a total of 3 times.

Fingernails:

200 mg twice daily for 7 days, followed by a treatment-free interval of 3 weeks, a total of twice.

or:

200 mg once daily for 3 months.

For treatment of special patient groups such as diabetic patients and patients with impaired immune systems, see section 4.4.

For skin infections, optimal clinical effects are reached 1-4 weeks after the cessation of treatment and for nail infections, 6-9 months after the cessation of treatment. This is because elimination of itraconazole from skin and nails is slower than from plasma.

Paediatric patients:

Experience of using the drug in children below the age of 12 years is limited, see section 4.4

Use in the elderly:

Since clinical data are limited, itraconazole should only be used in the elderly if the potential benefit is estimated to outweigh the potential risk.

Impaired hepatic function:

Itraconazole is mainly metabolised in the liver. The terminal half-life is somewhat prolonged and the bioavailability is reduced in patients with cirrhosis. A dose adjustment should be considered for these patients. Monitoring of plasma levels may be necessary (see section 4.4)

Impaired renal function:

The plasma level in patients with renal insufficiency may become sub-therapeutic. Experience is limited with respect to dose adjustment in these patients. Monitoring of plasma levels may be necessary. Itraconazole cannot be removed by dialysis.

Decreased gastric acidity:

Absorption of itraconazole is impaired when gastric acidity is decreased. Refer to section 4.4 for information regarding the treatment of patients with achlorhydria and patients taking acid secretion inhibitors or acid neutralising medicinal products.

Patients with AIDS and neutropenia

Impaired absorption in AIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. In these patients, blood level monitoring and if necessary dose adjustment might be indicated, see section 4.4.

4.3 Contraindications

Hypersensitivity to itraconazole or to any of the excipients.

Itraconazole should be administered to pregnant women only in life-threatening situations and only when the potential benefit outweighs the potential harm to the foetus.

Concomitant treatment with terfenadine, astemizole, mizolastine, cisapride, triazolam and oral midazolam, dofetilide, quinidine, pimozone, ergot alkaloids (e.g. ergotamine and dihydro-ergotamine) as well as CYP3A4 metabolised HMG-CoA reductase inhibitors, such as lovastatin, simvastatin and atorvastatin (see section 4.5).

4.4 Special warnings and precautions for use

Transient, asymptomatic decreases in left ventricular ejection fraction were observed in a healthy volunteer study of intravenous itraconazole.

Itraconazole has been shown to have a negative inotropic effect and has been associated with reports of congestive heart failure. Itraconazole 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. The risk-benefit assessment should consider factors such as the severity of the indication, the dosage regimen, the duration of treatment and individual risk factors for congestive heart failure. Patients with these risk factors should be informed of the signs and symptoms of congestive heart failure. Caution should be exercised during treatment and the patient should be monitored for the signs and symptoms of congestive heart failure. Itraconazole should be discontinued if such signs or symptoms occur during treatment.

Caution is warranted when co-administering itraconazole and calcium channel blockers (see section 4.5).

Itraconazole is a potent inhibitor of CYP3A4. Co-administration of itraconazole and medicinal products metabolised via CYP3A4 may therefore result in markedly increased plasma levels of such drugs (see sections 4.3 and 4.5).

Itraconazole should not be used during treatment and for two weeks following treatment cessation with CYP3A4-inducers (such as rifampicin, rifabutin, phenytoin, phenobarbital, carbamazepine, St. John's Wort). Concomitant administration with these medicinal products may result in sub-therapeutic levels of itraconazole and therefore risks treatment failure (see section 4.5).

Absorption of itraconazole is impaired when gastric acidity is decreased. Acid neutralising drugs (e. g. aluminium hydroxide) should be administered at least 2 hours after the intake of itraconazole capsules. Patients with achlorhydria such as certain AIDS patients and patients taking acid secretion suppressors (such as H₂-antagonists and proton-pump inhibitors) are advised to take itraconazole with an acidic beverage, since adequate absorption requires a low pH in the stomach.

Very rare cases of severe hepatotoxicity, including some cases of fatal acute liver failure, have been reported in patients treated with itraconazole. Some of these cases involved patients who had no pre-existing liver disease and some have been observed within the first month of treatment, including the first week. Liver function monitoring should be considered in patients taking itraconazole. Patients should be instructed to promptly report to their physician any 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. Most cases of severe hepatotoxicity involved patients being treated for systemic indications and/or had pre-existing liver disease or had other significant medical conditions and/or were taking other hepatotoxic drugs. In patients with raised liver enzymes or an existing liver disease, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit outweighs the risk of hepatic injury. In such cases, liver enzyme monitoring is necessary.

There is no information regarding cross-hypersensitivity between itraconazole and other antimycotic azoles. Caution should however be exercised while prescribing Itraconazol Actavis capsules to patients hypersensitive to other azoles.

Experience is limited with respect to pulse therapy in diabetic patients and patients with impaired immune systems (see section 5.2).

The effect of pulse therapy has not been studied in children.

There is only little clinical experience of using itraconazole in children. Itraconazol Actavis 100 mg capsules should therefore not be administered to children, except in cases where the expected positive effects outweigh the potential risks.

Itraconazol Actavis contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take this medicine.

In cases where neuropathy attributed to itraconazole occurs, treatment should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of itraconazole on other medicines:

Itraconazole is a potent inhibitor of CYP3A4 and inhibits the metabolism of medicines which are metabolised by this enzyme. This can result in an increase and/or a prolongation of their effects, including undesirable effects. Thus, itraconazole should not be used in combination with other drugs metabolised by CYP3A4 unless the plasma levels, effects or undesirable effects of the co-administered drug are closely monitored.

Itraconazole can inhibit the transport protein p-glycoprotein (P-gp), resulting in increased plasma level of P-gp substrate such as digoxin. If concomitant treatment with digoxin is necessary, the digoxin plasma levels must be closely monitored.

Contraindicated combinations:

Terfenadine:

Itraconazole inhibits the metabolism of terfenadine. Cases of cardiac effects, such as *torsades de pointes*, have been reported in patients treated concomitantly with this drug.

Astemizole:

Concomitant treatment with itraconazole (400 mg/day for two weeks) has been observed to increase astemizole's AUC_{0-∞} threefold and to increase the terminal half-life (from 2.1 to 3.6 days).

Pimozide, cisapride:

When used concomitantly azole antimycotics such as itraconazole inhibit the metabolism and thus increase the serum level of these drugs. This can lead to QT prolongation, cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and *torsades de pointes*.

Triazolam, oral midazolam:

Concomitant treatment with itraconazole (200 mg/day) has been observed to produce a 27-fold increase in triazolam's AUC. A 10-fold increase in AUC is observed with midazolam.

Dofetilide, mizolastine:

Concomitant treatment with itraconazole may result in markedly increased plasma concentrations of dofetilide and mizolastine resulting in a higher risk of adverse events.

Quinidine:

Concomitant treatment with itraconazole (200mg/day) has been observed to produce a 2.4-fold increase in quinidine's AUC.

HMG-CoA reductase inhibitors metabolised by CYP3A4 such as simvastatin and atorvastatin:

Itraconazole inhibits the metabolism of simvastatin which may result in a more than 10-fold increase in the exposure to the active metabolite simvastatin acid. The metabolism of atorvastatin is inhibited when itraconazole is used concomitantly resulting in a 3-fold increase of its AUC.

Ergot alkaloids (e.g. ergotamine and dihydro-ergotamine):

Itraconazole inhibits the CYP3A4-catalysed metabolism of ergot alkaloids. This may lead to severe vasoconstriction (ergotism) which can cause necrosis in arms and legs.

Concomitant use of the following medicinal products may require dose adjustment:

Caution should be exercised when co-administering itraconazole and other medicinal products metabolised by CYP3A4. The plasma levels, effects or adverse events should be monitored and the dose possibly reduced in patients receiving itraconazole concomitantly with the medicines listed below.

CYP3A4 metabolised calcium channel blockers such as dihydropyridines and verapamil:

Caution is warranted when co-administering itraconazole with calcium channel blockers. In addition to possible pharmacokinetic interactions involving the drug metabolising enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In an interaction study involving the administration of 200 mg itraconazole once daily for four days followed by a dose of 5 mg felodipine, a 6-fold increase in AUC and an 8-fold increase in C_{max} for felodipine were reported.

Oral anticoagulants

Preliminary observations indicate that itraconazole may potentiate the effect of warfarin. Careful monitoring of the prothrombin time is necessary with this combination.

HIV protease inhibitors such as ritonavir, indinavir, saquinavir:

No experimental studies have been performed, but since protease inhibitors are mainly metabolised via CYP3A4, co-administration of itraconazole is likely to lead to elevated plasma concentrations of these drugs.

Certain antineoplastic agents such as vinca alkaloids, busulphan, docetaxel and trimetrexate:

Itraconazole can inhibit the metabolism of these agents. Busulphan's clearance was reduced by 20% with concomitant use of itraconazole.

Certain immunosuppressive agents: cyclosporin, tacrolimus, sirolimus:

Concomitant use with itraconazole may result in markedly increased plasma concentrations of these agents resulting in adverse events. The plasma concentrations of cyclosporin, tacrolimus and sirolimus, should be monitored when these drugs are used in combination with itraconazole.

Digoxin and P-gp substrates:

Itraconazole also seems to inhibit P-gp. Case reports show that administration of itraconazole to patients treated with digoxin can result in markedly increased plasma levels of digoxin with symptoms of digoxin intoxication. Itraconazole decreases the renal clearance of digoxin probably through inhibition of P-gp which is responsible for the active secretion of digoxin. The digoxin plasma levels must be closely monitored if concomitant treatment with the two drugs is necessary,

Dexamethasone:

Itraconazole reduces the clearance of intravenous dexamethasone by 68% by inhibiting CYP3A4.

Methylprednisolone:

Itraconazole reduces the metabolism of methylprednisolone. A 4-fold increase of its AUC and a doubling of the half-life have been observed. The risk of steroid side effects is increased particularly during long term concomitant therapies in which the methylprednisolone dose is not reduced.

Alprazolam:

Itraconazole has been observed to induce a 60% inhibition of alprazolam's clearance resulting in potentiated effects.

Buspirone:

Itraconazole increases buspirone's bioavailability (oral single dose) 19-fold. For combination treatment the buspirone dose must be drastically reduced.

Other: Carbamazepine, alfentanil, brotizolam, midazolam (intravenous), rifabutin, ebastine, reboxetine:

Itraconazole inhibits the metabolism of these agents. However, the clinical relevance of such an interaction is uncertain.

It should be noted that the above information regarding CYP3A4 substrate is not a complete list and that itraconazole can interact with other medicinal products metabolised by CYP3A4.

Effects of other medicines on itraconazole:

Itraconazole is mainly metabolised via cytochrome CYP3A4. Interaction studies have been conducted with rifampicin, rifabutin and phenytoin, which are potent inducers of CYP3A4. The bioavailability of itraconazole and hydroxy-itraconazole in these studies was decreased to such an extent that the drug's efficacy was largely reduced. Co-administration with enzyme inducers (rifampicin, rifabutin, phenytoin, phenobarbital, carbamazepine) is therefore not recommended. Since similar interactions are also expected with St. John's Wort (*Hypericum Perforatum*), concomitant use of the two drugs should be avoided.

Rifampicin:

Rifampicin has been shown to induce the metabolism of itraconazole resulting in significantly reduced (60-90%) plasma levels of itraconazole. Thus when these drugs are used concomitantly, the desired antifungal effects might not be achieved.

Rifabutin:

Itraconazole's C_{max} and AUC were reduced by 70-75% when used together with rifabutin. A case report suggests a kinetic interaction resulting in an increase in serum rifabutin levels and a risk in developing uveitis when given concomitantly with itraconazole. Such combination treatment should therefore be avoided.

Phenytoin:

After daily administration of 300 mg phenytoin for 15 days, the AUC for a 200 mg dose of itraconazole decreased by more than 90%. Itraconazole's half-life decreased from 22.3 hrs to 3.8 hrs.

CYP3A4 inhibitors:

Potent inhibitors of CYP3A4 such as ritonavir, indinavir, clarithromycin and erythromycin can increase the bioavailability of itraconazole.

Omeprazole, esomeprazole:

Co-administration of omeprazole and itraconazole results in a reduction of itraconazole's plasma concentration and AUC by approx. 65%, probably due to reduced absorption which is pH-dependent. It is assumed that esomeprazole would interact in a similar manner.

4.6 Pregnancy and lactation

Pregnancy

When itraconazole was administered in high doses to pregnant rats (40 mg/kg/day or higher) and mice (80 mg/kg/day or higher), there was an increase in the incidence of foetal abnormalities and adverse effects on the embryo.

No studies of the use of itraconazole in pregnant women are available. Itraconazole Actavis capsules should not be given to pregnant women except in life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus.

Fertile women

Women of childbearing potential using itraconazole should take adequate contraceptive precautions until their first menstrual period following the end of itraconazole therapy.

Breast-feeding

Very small amounts of itraconazole are excreted in human milk. The expected benefits of treatment with Itraconazol Actavis capsules should therefore be weighed against the potential risk associated with breast-feeding. In case of doubt the patient should not breast-feed.

4.7 Effects on ability to drive and use machines

No effects have been observed.

4.8 Undesirable effects

It is expected that approximately 9% of patients will experience adverse reactions while taking itraconazole. In patients receiving prolonged (approximately 1 month) continuous therapy, the incidence of adverse events was higher (about 15%). The most frequently reported adverse experiences were of gastrointestinal, hepatic and dermatological origin. The table below ranks adverse reactions within each system organ class under headings of frequency using the following convention: Common (>1/100), rare (>1/10000, <1/1 000) and very rare (<1/10 000, isolated cases included).

Frequency	Common (>1/100)	Rare (>1/10000, <1/1 000)	Very rare (<1/10 000, including isolated reports)
Organ system			
Immune system disorders			Anaphylactic, anaphylactoid and allergic reactions
Metabolic and nutritional disorders			Hypokalaemia, hypertriglycerid-aemia
Nervous system disorders			peripheral neuropathy
Cardiac disorders			congestive heart failure
Respiratory, thoracic and mediastinal disorders			pulmonary oedema
Gastrointestinal disorders	abdominal pain, vomiting, dyspepsia, nausea, diarrhoea and constipation		
Hepato-biliary disorders		hepatitis and reversible increases in hepatic enzymes	fatal acute liver failure, severe hepatotoxicity
Skin and subcutaneous tissue disorders		allergic reactions such as rash, pruritus, urticaria and angio-oedema	Stevens-Johnsons syndrome, alopecia
Reproductive system and breast disorders		menstrual disorders	

General disorders and conditions related to site of administration	headache, dizziness		oedema
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4.9 Overdose

Symptoms. Nausea, abdominal pain, dizziness, headache and other adverse reactions described above may occur and be intensified (see section 4.8 Undesirable effects).

Treatment. Gastric lavage may be performed within the first hour after ingestion. Activated charcoal can be given if considered appropriate. Otherwise symptomatic treatment should be instituted. Itraconazole cannot be removed by haemodialysis. No specific antidote is available. Itraconazole cannot be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivative
ATC-code: J02AC02

Itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is a vital cell membrane component in fungi and impairment of its synthesis ultimately results in an antifungal effect.

In vitro studies have shown that itraconazole inhibits the growth of a variety of human pathogenic fungi at concentrations usually ranging from ≤ 0.025 to $0.8 \mu\text{g/ml}$. Examples are: *Candida albicans*, many *Candida non-albicans spp.*, *Aspergillus spp.*, *Trichosporon spp.*, *Geotrichum spp.*, *Cryptococcus neoformans*, dermatophytes and many fungi belonging to the dematiaceae family such as *Fonsecaea spp.*, *Histoplasma spp.*, *Pseudallescheria boydii* and *Penicillium marneffeii*.

Candida glabrata and *Candida tropicalis* are usually the least sensitive *Candida*-species with some isolates showing clear resistance to itraconazole *in vitro*. The following types of fungi are not inhibited by itraconazole: *Zygomycetes* (i.e. *Rhizopus spp.*, *Rhizomucor spp.*, *Mucor spp.*, *Absidia spp.*), *Fusarium spp.*, *Scedosporium spp.* and *Scopulariopsis spp.*

5.2 Pharmacokinetic properties

Since itraconazole displays non-linear pharmacokinetics, a doubling of the dose will result in an almost 3-fold increase of the plasma concentration. The absolute bioavailability of an oral solution is 55%.

The bioavailability of Itraconazol Actavis capsules is maximal when the capsules are taken immediately after a meal. However, the bioavailability is subject to large inter- and intraindividual variations. Peak plasma levels are reached 3 to 4 hours after an oral dose has been administered and steady state attained after 1 to 2 weeks of treatment. The plasma protein binding is 99.8%. Concentrations of itraconazole in whole blood are approx. 60% of those in the plasma. Uptake in keratinous tissues, especially the skin, is up to 4 times higher than in plasma. The elimination of itraconazole from the skin is related to epidermal

regeneration. Therapeutic levels persist for 2 to 4 weeks after discontinuation of a 4-week treatment. Detectable levels in nail keratin persist for at least 6 months after the end of a 3-month course of therapy. Fungicidal levels of itraconazole in the vaginal epithelium persist for 3 days after the end of treatment. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be 2 to 3 times higher than the corresponding plasma concentrations. After intravenous administration of itraconazole, total plasma clearance is approx. 380 ml/min and the distribution volume is approx. 11 L/kg. Plasma itraconazole is eliminated biphasically with a terminal half-life of 24 to 36 hours.

Itraconazole is extensively metabolised by the liver into a large number of metabolites. One of the metabolites is hydroxy-itraconazole which has a comparable antifungal activity *in vitro* to itraconazole. Fungicidal levels measured by bio-assay were about 3 times those of itraconazole assayed by high-performance liquid chromatography (HPLC). 3 to 18% of the dose is excreted in faeces as unchanged substance. Excretion in urine is less than 0.03%. About 35% of a single dose is excreted as metabolites in urine within 1 week. Patients with impaired renal function or impaired immune system (e.g. in case of neutropenia or AIDS) may have a lower bioavailability of itraconazole (see section 4.4). Itraconazole inhibits human CYP3A4 (see also section 4.5).

5.3 Preclinical safety data

There are no relevant preclinical safety data which may be added to the safety evaluation as divulged in other sections of this SPC.

6 PHARMACOKINETIC PROPERTIES

6.1 List of excipients

Sugar spheres (sucrose and maize starch)
Poloxamer
Hypromellose

Capsule shell:

Gelatin
Colouring agents (indigo carmine (E 132), quinoline yellow (E 104) and titanium dioxide (E 171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Aluminium/Aluminium blisters: 4, 6, 15, 18, 28, 30 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group hf.
Reykjavíkurvegur 76-78,
220 Hafnarfjörður,
Iceland

8 MARKETING AUTHORISATION NUMBER(S)

MA651/00101

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3rd August 2006.

10 DATE OF REVISION OF THE TEXT

N/A