Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole Actavis 100 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg fluconazole.

Excipient:
Each hard capsule contains 82 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Fluconazole Actavis 100 mg consists of light blue cap and white body, size “2” hard gelatine capsules, filled with white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fluconazole Actavis is indicated for treatment of following infections caused by fungi which are known to be or are likely to be susceptible to fluconazole:
- Acute and recurrent vaginal candidiasis when systemic therapy is considered appropriate.
- Verified fungal infections of the skin such as tinea corporis/tinea cruris/tinea pedis (caused by dermatophytes), tinea versicolor or candidiasis when topical treatment has not succeeded or is considered inadequate. Fluconazole should only be used to treat tinea versicolor when the infection is resistant to first line therapy or when the patient is immunocompromised.
- Mucosal candidiasis, including oropharyngeal, oesophagal, mucocutaneous and non-invasive bronchopulmonary candidiasis.
- Candiduria in immunocompromised patients.
- Systemic candidiasis (candidaemia, disseminated deep candidiasis, peritonitis) in non-neutropenic patients.
- Prophylaxis of *Candida* infections in patients with neutropenia (e.g. due to AIDS or bone marrow transplantation).
- Treatment and maintenance therapy to prevent relapse of cryptococcal meningitis in immunocompromised patients.

Paediatric use
Fluconazole Actavis should not be used for tinea capitis.
Not all indications are applicable for paediatric patients; see details in section 4.2.
Consideration should be given to official guidance on the appropriate use of antifungal agents.

4.2 Posology and method of administration

The daily dose of fluconazole depends on the type and severity of the fungal infection. The treatment of infections requiring multiple dosing must be continued until clinical parameters or laboratory results show that the active fungal infection has declined. An insufficient treatment period may lead to recurrence of the active infection.

Depending on the severity of the disease and the clinical state of the patients of the disease intravenous administration may be required. It is not necessary to change the daily dose of fluconazole when changing the route of administration from intravenous to oral.

Adults:
Vaginal candidiasis: 150 mg as a single dose.

Verified fungal infections of the skin: Tinea corporis, tinea cruris, tinea pedis, tinea versicolor: 150 mg once weekly for 4 – 6 weeks.

Mucous membrane candidiasis: Oropharyngeal candidiasis: Normal dose is 50-100 mg daily for 7 to 14 days. Duration of treatment depends on clinical response.

Oesophageal mucocutaneous and non-invasive bronchopulmonary candidiasis: Normal dose is 50 mg daily for 14 to 30 days. In severe and particular recurrent cases the dose can be increased to 100 mg.

Candiuria in immunocompromised patients: Normal dose is 50 mg daily for 14 to 30 days. In severe cases the daily dose can be increased to 100 mg fluconazole.

Systemic candidiasis: The dose in candidaemia and other invasive candida infections is 400 to 800 mg on the first day and 200 to 400 mg daily therafter. The dose depends on the type and severity of the infection. In most cases a loading dose of 800 mg on the first day followed by 400 mg daily thereafter may be preferable. The duration of treatment, often up to several weeks, is determined by the clinical response.

Prophylaxis of candida infections in patients with neutropenia: 400 mg once daily. The treatment should be initiated a few days before neutropenia occurs and should continue until 7 days after neutrophil counts have increased to >1 x 10^9/l.

Treatment and maintenance treatment of cryptococcal meningitis in immunocompromised patients: Initially 400 mg on the first day followed by 200 to 400 mg once daily. Duration of treatment for cryptococcal infections depends on the clinical response, but is usually at least 6 to 8 weeks for cryptococcal meningitis.

A daily dose of 200 mg is recommended in order to avoid recurrence of cryptococcal meningitis. Duration of maintenance treatment in AIDS patients should be carefully justified due to the high risk of resistance to fluconazole.

Paediatric use:
The capsules are clearly unsuitable for children younger than 5-6 years, who cannot take oral medication. As with similar infections in adult, the duration of treatment is based on the clinical and mycological response. Fluconazole is administered as a single daily dose.

For children with impaired renal function, see dosing in “Patients (adults and paediatric) with impaired renal function”.

Children over four weeks of age
The recommended dose of fluconazole for mucosal candidiasis is 3 mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly.
For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6-12 mg/kg daily, depending on the severity of the disease.
For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3-12 mg/kg daily, depending on the extent and duration of induced neutropenia (see adult dosing).

A maximum dosage of 400 mg daily should not be exceeded in children.

Children four weeks of age and younger
Neonates excrete fluconazole slowly. In the first two weeks of life, the same mg/kg dosing as in older children should be used but administrated every 72 hours.
During weeks 3 and 4 of life, the same dose should be given every 48 hours. There are few PK data to support this posology in term newborn babies (see section 5.2).

A maximum dosage of 12 mg/kg every 72 hours should not be exceeded in children in the first two weeks of life. For children between 3 and 4 weeks of life, 12 mg/kg every 48 hours should not be exceeded.

Elderly:
Patients without impaired renal function usually receive normal dosing. The dosage to patients with impaired renal function (creatinine clearance <50 ml/min) is given below.

Patients (adults and paediatric) with impaired renal function:
Fluconazole is mainly excreted unchanged in the urine. Change of single-dose regimen is not required.
Patients with renal impairment given multiple doses of 50-400 mg should be given the recommended dose for the indication the first day, after which the daily dose (depending on therapeutic indication) should be based on the following table:

Creatinine clearance (ml/min)	**Percentage of recommended dose**
> 50	100%
11-50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

The pharmacokinetics of fluconazole has not been studied in children with renal insufficiency.

Method of administration
The capsules must be swallowed whole with a sufficient amount of fluid (e.g. one glass of water) and can be taken independently of food.

4.3 Contraindications

- Hypersensitivity to fluconazole, other azole derivatives or to any of the excipients.

- Co-administration with drugs both known to prolong the QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine (see also section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Local guidelines for the use of antifungals should be followed (see section 4.1 and 5.1).

In rare cases severe hepatotoxicity including death has been reported, primarily in patients suffering from serious underlying diseases. No obvious causal relationship between hepatotoxicity and the total daily dose of fluconazole, duration of treatment, or the patient’s gender or age has been observed.

Patients who develop abnormal liver test values or significant increases of originally abnormal levels during treatment with fluconazole must be monitored closely. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment.
The treatment with fluconazole should be discontinued if there is clinical evidence of development of a liver disease caused by fluconazole. In most cases, liver toxicity has been reversible at discontinuation of the treatment.

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to development of severe cutaneous reactions to many medicinal products. If a rash develops in a patient treated for a superficial fungal infection that is considered attributable to fluconazole, the therapy with fluconazole should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.

As with other azoles, anaphylactic reactions have been reported in rare cases (see section 4.8).

Some azoles, including fluconazole, have been associated with prolongation of the QT interval. Rare cases of QT

prolongation and Torsade de pointes have been observed during treatment with fluconazole. Although the association of fluconazole and QT-prolongation has not been fully established, fluconazole should be used with caution in patients with potentially proarrythmic conditions such as:
- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrythmias
- Electrolyte disturbances, particularly hypokalaemia and hypomagnesaemia
- Concurrent treatment with medicines known to prolong the QT interval but are not metabolised by CYP3A4 (see section 4.5).

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of fluconazole treatment.

Dose reduction of fluconazole is required if creatinine clearance is below 50 ml/min (see section 4.2).

In women of child-bearing potential, appropriate contraceptive measures should be considered in case long-term treatment is indicated (see section 4.6).

Patients receiving treatment with fluconazole doses below 400 mg per day and terfenadine should be monitored closely (see section 4.3 and section 4.5).

Fluconazole is a potent cytochrome P450 (CYP) isoenzyme 2C9 inhibitor and a moderate CYP3A4 inhibitor. Patients who concurrently with fluconazole are treated with medicinal products with a narrow therapeutic index, e.g. warfarin and phenytoin, that are metabolised via CYP2C9 and CYP3A4, must be monitored (see section 4.5).

Fluconazole Actavis capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations with fluconazole are contraindicated:

Cisapride (CYP3A4 substrate)
There have been reports of cardiac events including Torsades de pointes in patients receiving fluconazole concomitantly with cisapride. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concurrent treatment with fluconazole and cisapride is contraindicated.

Terfenadine (CYP3A4 substrate) with doses of 400 mg fluconazole or higher
Severe cardiac dysrhythmias secondarily to prolongation of the QTc interval in patients on treatment with azole products concomitantly with terfenadine have been observed.
One study with 200 mg fluconazole once daily and concurrent treatment with terfenadine did not show any prolongation of the QTc interval.
Another study with 400 mg and 800 mg fluconazole once daily showed that fluconazole 400 mg or more daily significantly increases the plasma level of terfenadine. Concomitant treatment with terfenadine and fluconazole in daily doses of 400 mg or more is contraindicated.
In treatment with fluconazole in doses below 400 mg per day the patient should be monitored closely.

Astemizole (CYP3A4 substrate)
Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. The resulting increased plasma concentrations of astemizole can lead to prolonged QT interval and severe ventricular arrhythmia, Torsades de pointes and cardiac arrest. Concomitant treatment with fluconazole and astemizole is contra-indicated due to the potential for serious, even fatal, cardiac effects.

Quinidine (CYP3A substrate)
Fluconazole may inhibit the metabolism of quinidine, leading to increased plasma concentrations and thus risk to prolongation of the QT interval.

Pimozide (CYP3A4-substrate)
Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of Torsade de pointes. Co-administration of fluconazole and pimozide is contraindicated.

Concurrent use of following other medicinal products is not recommended:

Erythromycin
There is an increased risk of cardiotoxicity (prolonged QT interval, Torsade de pointes) and thus sudden cardiac death when using fluconazole and erythromycin concomitantly. The combination should be avoided.

Concurrent use of following other medicinal products requires measures and dose adjustments:

Medicinal products affecting the metabolism of fluconazole

Hydrochlorothiazide
In a pharmacokinetic interaction study with healthy volunteers, co-administration of fluconazole and multiple-doses of hydrochlorothiazide increased the plasma concentrations of fluconazole by 40%. This does not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.

Rifampicin (CYP450 inducer)
Concomitant intake of fluconazole and rifampicin resulted in a 25% reduction of AUC and 20% shorter half-life of fluconazole due to hepatic enzyme induction. Increase of dosage should be considered in patients concomitantly receiving rifampicin.

Didanosine
Although concomitant intake of didanosine and fluconazole appears have little effect on didanosine pharmacokinetics or efficacy, the response of fluconazole should be monitored. It may be advantageous to administer fluconazole prior to didanosine.

Effect of fluconazole on the metabolism of other medicinal products

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Besides the observed/documented interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot alkaloids, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored.
The enzyme inhibiting effect of fluconazole may persist for 4-5 days following discontinuation of fluconazole treatment due to the long fluconazole half-life.

Alfentanil (CYP3A4 substrate)
A study observed a reduction in clearance and distribution volume as well as prolongation of t½ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline
Fluconazole increases the effect of amitriptyline and nortriptyline. S-nortriptyline and/or A-amitriptyline may be measured at initiation of combination treatment and after one week. The dose of amitriptylin/nortriptylin should be adjusted if necessary.

Anticoagulants (CYP2C9 substrate)
In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting) (CYP3A4 substrate)
Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, Cmax with 20-32% and increases t½ by 25-50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

Calcium channel antagonists (CYP3A4 substrates)
Certain dihydropyridine calcium channel antagonists (nifedipine, isradipine, nicardipine, amlodipine and felodipine) are metabolised by CYP3A4. Substantial peripheral oedema and/or increased calcium antagonist serum levels has been described in literature when itraconazole and felodipine, isradipine or nifedipine are co-administered. Such interaction could also occur with fluconazole.

Carbamazepine
Fluconazole inhibits the biotransformation of carbamazepine and an increase of about 30% in serum carbamzepine is seen. There is a risk of development of carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Celecoxib (CYP2C9 substrate)
In a clinical study, concomitant treatment with fluconazole 200 mg daily and celecoxib 200 mg resulted in an 68% and 134% increase in celecoxib Cmax and AUC, respectively. The interaction is believed to be due to inhibition of cytochrome P450 2C9 metabolism of celecoxib. Halving the celecoxib dose is recommended to patients concurrently treated with fluconazole.

Ciclosporin (CYP3A4 substrate)
Clinically significant interactions with ciclosporin have been shown at fluconazole doses of 200 mg and higher. In a pharmacokinetic study with renal transplant patients receiving fluconazole 200 mg daily and ciclosporin 2.7 mg/kg/day, there was a 1.8-fold increase in ciclosporin AUC and a 55% decrease in clearance. It is recommended to follow the ciclosporin plasma concentrations in patients on treatment with fluconazole.

Cyclophosphamide
Combination treatment with cyclophosphamide and fluconazole results in increase in serum bilirubin and serum creatinine. The combination can be used when increased attention is given to the risk of increase in serum bilirubin and serum creatinine.

Fentanyl
Fluconazole may increase the concentration of fentanyl and thus the risk of opioid intoxication. The mode of action is thought to be inhibition CYP3A4 by fluconazole. One fatal case of possible fentanyl fluconazole interaction has been reported. The author judged that the patient died from fentanyl intoxication.
Furthermore, in a randomized crossover study with twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Dose adjustment of fentanyl may be necessary.

Halofantrine (CYP3A4 substrate)
Drugs that inhibit CYP3A4 lead to an inhibition of halofantrine metabolism.

HMG-CoA reductase inhibitors (CYP2C9 or CYP3A4 substrates)
The risk of myopathy is increased when fluconazole is administered concurrently with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Up to 200% individual increases in the area under the curve (AUC) of fluvastatin may occur as a result of the interaction between fluvastatin and fluconazole. Caution is warranted if concurrent administration of fluconazole and HMG-CoA reductase inhibitors is deemed necessary. The combination may require a dose reduction of the HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy or rhabdomyolysis and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

Losartan (CYP2C9 substrate)
Fluconazole inhibits the biotransformation of losartan into its active metabolite (E-3174) which is responsible for the major part of the angiotensin-II receptor antagonism that occurs during losartan treatment. Concomitant treatment with fluconazole might lead to increased concentrations of losartan and decreased concentrations of the active metabolite. It is recommended that patients receiving the combination be monitored for continued control of their hypertension.

Methadone
Fluconazole may increase the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs
The Cmax and AUC of flurbiprofen was increased by 23% and 81%, respectively, when co-administered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.
Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Oral contraceptives
Two pharmacokinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50 mg fluconazole study, while at 200 mg daily the AUCs of ethinyloestradiol and levonorgestrel were increased 40% and 24%, respectively. Thus multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Phenytoin (CYP2C9 substrate)
Fluconazole inhibits the hepatic biotransformation of phenytoin. Intake of fluconazole 200 mg concomitantly with phenytoin 250 mg intravenously increased the phenytoin AUC by 75% and Cmin by 128%. If it is necessary to administer both substances concomitantly, the phenytoin concentration must be controlled, and the phenytoin dose adjusted, in order to avoid toxic concentrations.

Prednisone (CYP3A4 substrate)
A liver transplant recipient receiving prednisone developed acute adrenal insufficiency when a three-month course of fluconazole was discontinued. The withdrawal of fluconazole caused probably an increase in CYP3A4 activity, leading to an increase in the degradation of prednisone. Patients receiving long-term therapy with fluconazole and prednisone should be closely monitored for signs of adrenal insufficiency when fluconazole is withdrawn.

Rifabutin (CYP3A4 substrate)
Fluconazole increases AUC of rifabutin by up to 80% resulting in increased serum concentrations of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered.

At combination therapy increased attention regarding symptoms of intoxication with rifabutin is recommended.

Saquinavir
Fluconazole increases AUC of saquinavir by approximately 50%, Cmax by approximately 55% and reduces clearance of saquinavir by approximately 50% due to inhibition of saquinavir’s hepatic transformation in CYP3A4 and P-

glycoprotein in the gut.

Dose adjustment of saquinavir may be necessary based on effect/concentration measurement.

Sulphonyl urea (CYP2C9 substrates)
Fluconazole increases the plasma concentrations of glibenclamide, gliclazide, glimpepiride, glipizide, chlorpropamide and tolbitamide when used concomitantly. Fluconazole and oral sulphonyl urea derivatives may be used concomitantly to diabetics, but the possibility of development of hypoglycaemia must be kept in mind and blood glucose levels closely monitored.

Tacrolimus and sirolimus (CYP3A4 substrates)
Concomitant intake of fluconazole and tacrolimus 0.15 mg/kg twice daily increased tacrolimus Cmin 1.4 and 3.1-fold with fluconazole doses of 100 mg and 200 mg, respectively. Renal toxicity has been reported in patients concomitantly receiving fluconazole and tacrolimus. Fluconazole may increase the serum concentrations of orally administered tacrolimus by up to 5-fold due to inhibition of the transformation of tacrolimus via CYP3A4 in the gut. No significant pharmacokinetic changes are seen if tacrolimus is given intravenously. The oral dose of tacrolimus should be reduced depending on concentration measurements.
Although no interaction studies have been conducted with fluconazole and sirolimus, a similar interaction as with tacrolimus might be expected. Patients who receive tacrolimus or sirolimus and fluconazole concomitantly must be closely monitored for tacrolimus/sirolimus plasma levels and toxicity.

Theophyllin
In a placebo controlled interaction study, the intake of fluconazole 200 mg for 14 days resulted in 18% decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed for theophyllin toxicity during fluconazole therapy. The treatment should be adjusted if signs of toxicity develop.

Vinca alkaloids
Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Trimetrexate
Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity should be closely monitored.

Vitamin A
Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Zidovudine
Fluconazole increases Cmax and AUC of zidovudine by 85% and 75%, respectively, due to a decrease in the oral clearance of zidovudione of about 45%. The half-life of zidovudine was also prolonged by approximately 128% at co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose adjustment of zidovudine may be considered.

Pharmacodynamic interactions

Medicinal products that prolong QT interval
Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concomitantly with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect cannot be excluded.

Amphotericin B
In vitro and *in vivo* animal studies have shown antagonism between amphotericin B and azole derivatives. The

mechanism of action of imidazoles is to inhibit ergosterol synthesis in fungal cell membranes. Amphotericin B acts by binding to sterols in the cell membrane and changing membrane permeability. Clinical effects of this antagonism are to date unknown, and a similar effect may occur with amphotericin B cholesteryl sulfate complex.

Interaction studies have shown that there is no clinical significant change in the absorption of fluconazole at oral use with food, cimetidine, antacids or following radiation therapy of the entire body in association with bone marrow transplantation.

4.6 Fertility, pregnancy and lactation

Pregnancy
Standard doses of fluconazole (<200 mg/day) and short-term treatment should not be given during pregnancy unless the benefits outweigh the foetal risk.
High doses of fluconazole and/or long-term treatment should only be given during pregnancy at life threatening infections.

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole administered as single or multiple doses during first trimester, do not indicate undesirable effects on the foetus.

Multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) have been reported in infants of mothers who were receiving treatment for at least 3 or several months with high doses (400-800 mg/day) of fluconazole for coccidioidomycosis. The causal relationship between fluconazole and these events has not been established.

Animal studies have shown teratogenic effects (see section 5.3).

Lactation
Fluconazole is excreted in human breast milk at concentrations lower than in plasma. Lactation can be continued following a single dose of 200 mg fluconazole or less. Lactation should be discontinued at treatment with fluconazole with multiple and/or higher doses.

Fertility
Data does not indicate undesirable effects on fertility in males or females. It has been demonstrated that intake of 50 mg fluconazole daily for up to 28 days did not affect the plasma concentrations of testosterone in men or steroid hormone concentration in women of child-bearing potential. 200 to 400 mg fluconazole per day has no clinical effect on endogeneous steroid levels or on ACTH stimulated response in healthy, male volunteers.

Fertile women should use adequate contraception during long-term treatment with fluconazole.

4.7 Effects on ability to drive and use machines

Fluconazole has no or negligible influence on the ability to drive and use machines. However when driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

4.8 Undesirable effects

Undesirable effects are listed below by body system organ class and by frequency.

The following frequency categories are used for classification of adverse effects:
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)

Not known (cannot be estimated from the available data).

System organ class / Frequency	Undesirable effects
Blood and lymphatic disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Anaemia. Agranulocytosis, leukopenia, neutropenia, thrombocytopenia.
Immune system disorders Rare (≥1/10,000 to <1/1,000)	Anaphylaxis
Metabolism and nutrition disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Anorexia, hypokalaemia. Hypercholesterolaemia, hypertriglyceridaemia.
Psychiatric disorders Uncommon (≥1/1,000 to <1/100)	Insomnia.
Nervous system disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	Headache. Dizziness, convulsions, paraesthesia, tremor, vertigo, somnolence, taste disturbances.
Cardiac disorders Rare (≥1/10,000 to <1/1,000)	Prolongation of the QT interval, Torsades de pointes (see section. 4.4).
Gastrointestinal disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	Abdominal pain, diarrhoea, nausea, vomiting. Flatulence, dyspepsia, dry mouth, constipation.
Hepatobiliary disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Increased alkaline phosphatase, AST, and ALT. Jaundice, cholestasis, hepatocellular damage, increased bilirubin. Hepatotoxicity (rarely fatal), hepatic failure, hepatitis, hepatocellular necrosis.
Skin and subcutaneous tissue disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Rash. Pruritus, urticaria, increased sweating. Angioedema, alopecia, face oedema, exfoliative cutaneous reactions including erythema multiforme, Stevens-Johnson syndrom and toxic

	epidermal necrolysis.
Musculoskeletal and connective tissue disorders Uncommon (≥1/1,000 to <1/100)	Myalgia.
General disorders and administration site conditions Uncommon (≥1/1,000 to <1/100)	Fatigue, malaise, asthenia, fever.

Paediatric population
The pattern and incidence of side effects and laboratory abnormalities recorded during paediatric use are comparable to those seen in adults.

4.9 Overdose

There have been reports of overdose with fluconazole.

Symptoms:
In one isolated case a 42 year old AIDS patients developed hallucinations and exerted paranoid behaviour following intake of 8200 mg fluconazole. The patient was hospitalised and recovered within 48 hours.

Treatment:
Symptomatic and supportive treatment and - if necessary - gastric lavage. Fluconazole is primarily excreted with the urine. Forced volume diuresis will probably increase the elimination rate. Three hours of haemodialysis will lower the plasma levels by approx. 50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives. ATC code: J02AC01

Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits the synthesis of the fungi's ergosterol, which is believed to lead to defects in the cell membrane. Fluconazole is highly specific for fungal cytochrome P-450 enzymes. Doses of fluconazole 50 mg daily for 28 days have not been shown to influence serum levels of testosterone in men or the steroid concentration in fertile women.

The spectrum of application includes a number of pathogens including *Candida albicans* and non-*Candida albicans* species, *Cryptococcus* species and dermatophytes. *Candida krusei* is resistant to fluconazole. Forty percent of *Candida glabrata* are primarily resistant to fluconazole. Infections caused by *Aspergillus*-species should not be treated with fluconazole.

The efficacy of fluconazole in tinea capitis has been studied in 2 randomised controlled trials in a total of 878 patients comparing fluconazole with griseofulvin. Fluconazole at 6 mg/kg/day for 6 weeks was not superior to griseofulvin administered at 11 mg/kg/day for 6 weeks. The overall success rate at week 6 was low (fluconazole 6 weeks: 18.3%; fluconazole 3 weeks: 14.7%; griseofulvin: 17.8%) across all treatment groups. These findings are not inconsistent with the natural history of tinea capitis without therapy.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of fluconazole are identical after i.v. and oral administration.

Absorption:
Fluconazole is well absorbed after oral administration. The absolute bioavailability is above 90%. The oral absorption

is not affected by concomitant food intake. The maximum fasting plasma concentration is achieved 0.5 – 1.5 hours after dose intake. 90% of the steady-state level is achieved 4-5 days after dosing once daily.

The plasma concentration is proportional to the dose:
Following administration of 200 mg of fluconazole, Cmax is around 4.6 mg/L and plasma concentrations at steady-state after 15 days are around 10 mg/L.
After administration of 400 mg of fluconazole, Cmax is around 9 mg/L and plasma concentrations at steady-state after 15 days are around 18 mg/L.

Administration of a double dose on day 1 results in plasma concentrations of approx. 90% of steady-state on day 2.

Distribution:
Distribution volume corresponds to the total body water. The plasma protein binding is low (11-12%).

Fluconazole is distributed over the total body water. The concentration in sputum corresponds to the plasma concentration. In patients with fungal meningitis the concentration of fluconazole in the cerebrospinal fluid is approx. 80% of the corresponding plasma concentration.

Higher levels of fluconazole are reached in stratum corneum, epidermis-dermis and in exocrine sweat than in serum. Fluconazole accumulates in stratum corneum. After 150 mg once a week the concentration of fluconazole in stratum corneum following 2 doses was 23.4 µg/g on day 7, and 7 days after the second dose still 7.1 µg/g.

Elimination:
Fluconazole is primarily eliminated via the kidneys. Approximately 80% of the administered dose will be excreted via the urine in a non-metabolised form. Fluconazole clearance is proportional with the creatinine clearance. No circulating metabolites were detected.

The plasma half-life is approx. 30 hours, which has created the basis for treatment with one single dose in vaginal candidiasis and a single dose once daily and once per week in connection with other indications.

It has been demonstrated that intake of 50 mg fluconazole daily for up to 28 days did not affect the plasma concentrations of testosterone in men or steroid hormone concentration in women of child-bearing potential. 200 to 400 mg fluconazole per day has no clinical effect on endogeneous steroid levels or on ACTH stimulated response in healthy, male volunteers.

Pharmacokinetics in children:
Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single dose studies, 2 multiple dose studies and a study in premature neonates. Data from 1 study were not interpretable due to changes in formulation partway through the study. Additional data were available from a compassionate use study.
After administration of 2 – 8 mg/kg fluconazole to children between ages of 9 months to 15 years, a AUC of about 38 µg.h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days – 11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75- 1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time, to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decrease with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

5.3 Preclinical safety data

Preclinical data from conventional studies on repeat-dose/general toxicity, genotoxicity or carcinogenicity indicate no special hazard for humans not already considered in other sections of the SmPC.

In reproduction toxicity studies in rat an increased incidence of hydronephrosis and extension of renal pelvis was reported and embryonal lethality was increased. An increase in anatomical variations and delayed ossification was noted as well as prolonged delivery and dystocia. In reproduction toxicity studies in rabbits abortions were recorded.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Lactose monohydrate
Maize starch, pregelatinised
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell**:**
Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister.
Pack sizes: 1, 2, 4, 6, 7, 10, 12, 14, 20, 21, 28, 30, 50, 60, 90, 100 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf,
Reykjavikurvegi 76-78,
220 Hafnarfjordur,
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/100/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 15th April 2011

10 DATE OF REVISION OF THE TEXT