IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1063/034/001
Case No: 2072834

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Niche Generics Limited

1 The Cam Centre, **Wilbury Way**, **Hitchin**, **Hertfordshire SG4 OTW**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Fluconazole Niche 2 mg/ml solution for Infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **03/12/2009** until **31/01/2013**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole Niche 2 mg/ml solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Solution for Infusion contains 2 mg of Fluconazole.
25 ml Solution for Infusion contains 50 mg Fluconazole
50 ml Solution for Infusion contains 100 mg Fluconazole
100 ml Solution for Infusion contains 200 mg Fluconazole
200 ml Solution for Infusion contains 400 mg Fluconazole

Excipients:
Each ml of Solution for Infusion contains 0.15 mmol (3.5 mg) sodium (as chloride)
25 ml Solution for Infusion contain 3.9 mmol (88 mg) sodium (as chloride)
50 ml Solution for Infusion contain 7.7 mmol (177 mg) sodium (as chloride)
100 ml Solution for Infusion contain 15.4 mmol (354 mg) sodium (as chloride)
200 ml Solution for Infusion contain 30.8 mmol (709 mg) sodium (as chloride)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
A clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
Treatment of mycoses caused by *Candida*, *Cryptococci* and other susceptible yeasts, in particular:

- Systemic candidiasis (including disseminated deep infections and peritonitis)
- Severe mucosal candidiasis (including oropharyngeal candidiasis, oesophageal candidiasis and non-invasive bronchopulmonary candidiasis), where oral treatment is not possible.
- Cryptococcal meningitis in adults
- Prophylaxis against deep *Candida* infections (especially *Candida albicans*) in patients with neutropenia due to bone marrow transplantation.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Before initiating treatment samples should be taken for microbiological analysis and the suitability of the therapy should subsequently be confirmed (see sections 4.2 and 5.1).

In some patients with severe cryptococcal meningitis the mycological response during fluconazole treatment may be slower compared to other treatments (see section 4.4).

Children and adolescents
Treatment of mycoses caused by *Candida* and other susceptible yeasts, in particular:

- Systemic candidiasis (including disseminated deep infections and peritonitis)
- Severe mucosal candidiasis (including oropharyngeal candidiasis, oesophageal candidiasis and non-invasive bronchopulmonary candidiasis), where oral treatment is not possible.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Before initiating treatment samples should be taken for microbiological analysis and the suitability of the therapy should subsequently be confirmed (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Treatment with fluconazole should be initiated by a physician experienced in the management of invasive fungal infections. The dose is dependent on the type and severity of the infection. The treatment of infections requiring multiple-dosing must be continued until clinical parameters or laboratory results show that the active infection has declined. An insufficient treatment period may lead to recurrence of the active infection.

Fluconazole is also available for oral therapy. The patient should be switched from dosing by the intravenous route to dosing by the oral route as soon as possible. It is not necessary to change the daily dose of fluconazole when changing the route of administration from intravenous to oral.

Adults:
Please refer to table 1 for specific dosage recommendations.

Elderly:
The normal adult dose should be given if there is no evidence of renal impairment. Please refer to table 1.

Table 1 – Guidance on the dose to the Admistrator for an adult treated by the Intravenous Route

Treatment with Fluconazole should be initiated by a physician experienced in the management of invasive fungal infections.

Indication	Initial daily dose (mg)	Subsequent daily dose (mg)	Recommended duration of treatment	Additional guidance
Systemic candidiasis				
Candidaemia, disseminated candidiasis and the other forms of invasive candida infection.	400-800	200-400	Dependant upon clinical response	The dose chosen must take into account local resistance patterns to fluconazole 9see section 5.1). Where the sensitivity of the pathogen has not yet been established, the higher dose should initially be considered. In most cases a loading dose of 800mg on the first day followed by

				400mg daily thereafter may be preferable.
Severe mucosal candidiasis				**Use only when oral dosing is not possible.**
Oropharyngeal candidiasis	100	100	7-14 days	In some cases a daily dose higher than 100mg may be required and treatment can be prolonged.
Other mucosal candida infections (except genital candidiasis)	100	100	14-30 days	The duration of maintenance treatment of AIDS patients should be balanced against the risk of resistance to fluconazole.
Treatment of cryptococcal meningitis				
Initial therapy	400	200-400	Typical 6-8 weeks	Duration of treatment will depend upon clinical and mycological response.
Prophylaxis against deep candida infections				
In patients with neutropenia due to bone marrow transplantation	400	400	See additional guidance	Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for seven days after the neutropil count rises above 1000 cells per mm^3 .

Paediatric use

Fluconazole 2 mg/ml Solution for Infusion should not be used in children and adolescents under the age of 16 years unless there is no therapeutic alternative, because efficacy and safety have not been sufficiently demonstrated.

Please refer to **Table 2** for specific dosage recommendations.

As with similar infections in adults, the duration of treatment is based upon the clinical and mycological response. Note that due to a slower elimination in newborn infants, the dosing intervals are increased.

There are few pharmacokinetic data to support this posology in newborn babies (see Section 5.2).

Table 2- Guidance On The Dose To Administer In Paediatrics Treated By The Intravenous Route.

Age Range	Indication(s)	Recommended dosage	Additional Guidance
Neonates	Note: There are few pharmacokinetic data to support the posologies in newborn babies. (see section 5.2)		
• 2 weeks or less	All indications listed below	6-12 mg/kg every 72 hours	A maximum dose of 12 mg/kg every 72 hours should not be exceeded in children in the first two weeks of life.
• 3-4 weeks	All indications listed below	6-12 mg/kg every 48 hours.	For children between 3 and 4 weeks of life, 12 mg/kg every 48 hours should not be exceeded.
Children aged 4 weeks and above	Note: For children aged five years or less the maximum daily dose should not exceed 400mg per day.		
	• Systemic candidiasis • Mucosal candidiasis	6-12mg/kg/day 3 mg/kg/day	On the first day a loading dose of 5mg/kg may be given in order to more rapidly reach steady state.

Patients with impaired renal function

Fluconazole is cleared primarily by renal excretion as unchanged drug. No adjustments in single dose therapy are necessary. In patients with impaired renal function (including children) who receive multiple dose therapy, the recommended initial loading dose can be given. After the loading dose, the daily dose (according to indication) based on the table below:

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

Table 3 – Dose Modifications Required Following the Initial Dose For Patients With Impaired Renal Function

(Further Dosage adjustments may be needed depending upon clinical condition)

Creatinine Clearance (ml/min)	Percent of Recommended Dose
>50	100%
11-50 (no dialysis)	50%
Patients receiving dialysis	100% after every dialysis session

Patients with liver insufficiency:
Fluconazole should only be administered with special care and under careful monitoring in patients with liver insufficiency (see section 4.4).

Interactions requiring dose adjustments:
Modifications to the dosing schedules provided in Tables 1 to 3 may be required where concomitant use of either rifampicin or hydrochlorothiazide is proposed.
Further details are provided in section 4.5.

Administration
For intravenous use as infusion. The product can be infused at a maximum rate of 10ml/min. In children the rate of intravenous infusion should not exceed 5ml/min. For premature infants the infusion time should be no less than 15 minutes. In patients requiring sodium- or fluid restriction, the rate of administration should be taken into consideration as Fluconazole consists of a salt solution. In such cases the infusion should be given over a longer period.

Fluconazole 2mg/ml solution for infusion is formulated in 0.9% sodium chloride solution; each 200 mg (100 ml bottle) contains 15 mmol of Na+ and 15 mmol Cl-. Consideration should be given to the rate of fluid administration in patients requiring sodium or fluid restriction.

Fluconazole may be administered either orally or by intravenous infusion. The route of administration selection will depend on the clinical condition of the patient.

For instructions on the handling of the product, see section 6.6.

4.3 Contraindications

Hypersensitivity to Fluconazole or other azole compounds or to any of the excipients. Fluconazole should not be co-administered with drugs both known to prolong the QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine. (see section 4.5).

4.4 Special warnings and precautions for use

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities of hepatic, renal, haematological and other biochemical function tests have been observed during treatment with Fluconazole 2mg/ml solution for infusion but the clinical significance and relationship to treatment is uncertain.

Severe liver toxicity, including death, has been reported in rare cases, most often in patients with serious underlying illnesses. No obvious connection, however, has been found between daily dose, duration of treatment, gender or age. Patients that develop abnormal liver function tests or significant increases from already abnormal levels during treatment should be carefully monitored.
Treatment should be discontinued if clinical signs of liver disease, with possible connection to fluconazole, develop. The liver toxicity has most often been reversible following withdrawal of the treatment. 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 dose of fluconazole must be reduced when creatinine clearance is below 50 ml/min (see section 4.2.).

Certain azoles, including fluconazole, have been associated with prolongation of the QT-interval. Rare cases of torsade de pointes have been reported during treatment with fluconazole. Even though a connection between fluconazole and prolonged QT-interval has not been formally confirmed, fluconazole should be administered with caution in patients with potentially pro-arrhythmic conditions such as:

- Congenital or documented acquired QT-prolongation
- Cardiomyopathy, particularly in the presence of heart failure
- Sinus bradycardia
- Symptomatic arrhythmias
- Electrolyte disturbances
- Concomitant administration of preparations known to prolong the QT-interval (see section 4.5).

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

In rare cases patients have developed exfoliative skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis in treatment with fluconazole. AIDS-patients have a higher tendency for the development of serious skin reactions from various drugs. Where patients with minor fungal infections that are being treated with fluconazole develop a skin rash, considered to be connected to treatment with fluconazole, the treatment should be stopped.

If patients who are being treated for invasive fungal infections or systemic infections develop a skin rash, they should be closely monitored and the treatment discontinued if bullous skin reactions or erythema multiforme develop.

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Patients who receive concomitant treatment with fluconazole and drugs which have a narrow therapeutic interval (e.g. warfarin and phenytoin) and which are metabolised via CYP2C9 and/or CYP3A4 should be closely monitored (see sections 4.3 and 4.5).

Fluconazole may lengthen the prothrombin time following administration of warfarin. Close monitoring of the prothrombin time is recommended.
Rare instances of anaphylactic reactions have been reported (see section 4.8).

Caution must be taken with patients with renal impairment, Please refer to section 4.2.

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

Data regarding efficacy and safety of fluconazole in children and adolescents less than 16 years of age are still limited. Therefore the benefits of the treatment with fluconazole should be carefully evaluated against the risks.

There are indications that by a portion of the patients treated with Fluconazole for cryptococcal meningitis, the mycologic response has been slower than with the treatment of amphotericin B in combination with flucytocin. This should be kept in mind when choosing treatment for patients with severe cryptococcal meningitis.

Patients concurrently receiving fluconazole at doses below 400 mg/day and terfenadine require close monitoring (see section 4.5).

This medicinal product contains 15.4 mmol (354 mg) sodium per 100 ml of solution. To be taken into account in patients on a controlled sodium diet and in cases where fluid restriction is required. Refer to section 2 for sodium contents in each pack size.

4.5 Interaction with other medicinal products and other forms of interaction

In addition to the interactions given below, there is a risk of elevated serum concentrations of other drugs metabolised via CYP2C9 and CYP3A4 with concomitant administration of fluconazole. Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Therefore caution should always be observed during combination therapy with medications such as these and the patient closely monitored. The effects may persist for 4-5 days due to the long half life of fluconazole.

The following combinations are contraindicated:
Astemizole (CYP3A4-substrate):
Astemizole overdoses have led to prolonged QT interval a severe ventricular arrhythmia, torsade de pointes and cardiac arrest. Concomitant administration of astemizole and fluconazole is contraindicated due to the potential for serious, potentially fatal, cardiac effects.

Cisapride (CYP3A4-substrate):
Cardiovascular effects, including torsade de pointes, have been reported in patients having received concomitant treatment with fluconazole and cisapride. In one controlled study, where 200 mg fluconazole was administered once daily concomitantly with cisapride 20 mg four times daily, a significant increase in plasma levels of cisapride and prolongation of the QTc-interval where achieved. Concurrent treatment with cisapride and fluconazole is contraindicated (see 4.3 Contraindications).

Terfenadine (400 mg fluconazole and higher; CYP3A4-substrate):
Serious cardiac arrhythmias, secondary to prolonged QTc- interval, have occurred in patients treated with anti-fungal medications such as triazolic compounds and terfenadine. Concomitant treatment with 200 mg fluconazole daily showed no prolongation of the QTc-interval. With doses of 400 mg and 800 mg fluconazole daily, the plasma concentration of terfenadine increased significantly. Concomitant treatment with fluconazole 400 mg per day or higher dose is contraindicated. With concomitant treatment with doses below 400 mg per day, the treatment should be closely monitored.

The effects of other drugs on fluconazole:
Hydrochlorothiazide:
The plasma concentration of fluconazole increased by 40 % with concomitant administration of hydrochlorthiazide in healthy volunteers. An increase of this dimension does not necessitate adjustment in the dose of fluconazole capsules in patients undergoing treatment with diuretics, but the prescribing doctor should be aware of the fact.

Rifampicin (CYP450-inducers):
Concomitant treatment with fluconazole (200 mg) and rifampicin (600 mg daily) reduced AUC for fluconazole by 23 % in healthy volunteers.
An increase in the dose of fluconazole should be considered in combination treatment.

The effects of fluconazole on other drugs:

Alfentanil (CYP3A4-substrate):
In concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers, AUC10 – increased twofold and clearance decreased by 55 % for alfentanil, probably through inhibition of CYP3A4. The combination may require dose adjustment.

Amphotericin B:
In-vitro and in-vivo animal studies have found 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. A similar effect may occur with amphotericin B cholesteryl sulfate complex.

Amitriptyline (CYP2D6-substrate):
Several case histories have described the development of elevated amitriptylline concentrations and signs of tricyclic toxicity when amitriptylline is used in combination with fluconazole. Concomitant infusion of fluconazole and nortriptylline, the active metabolite of amitriptylline, has been reported to lead to increased nortriptylline levels. Due to the risk of amitriptylline toxicity, monitoring of amitriptylline levels should be considered with dose adjustment where indicated.

Anticoagulants (CYP2C9-substrate):
In concomitant treatment with fluconazole and warfarin, the prothrombin time increased up to twofold. This is probably due to an inhibition of the metabolism of warfarin via CYP2C9. The prothrombin time should be monitored closely in patients treated concomitantly with fluconazole and coumarin-type anticoagulants.

Benzodiazepines (CYP3A4-substrate):
Fluconazole may inhibit the metabolism of benzodiazepines metabolised via CYP3A4, e.g. midazolam and triazolam. In concomitant oral single dose treatment with fluconazole (400 mg) and midazolam (7.5 mg) AUC increased 3.7 times and the half life of midazolam 2.2 times. The combination should be avoided. Where concomitant treatment is considered necessary, a reduction in the dose of midazolam should be considered and the patient monitored closely In concomitant treatment with fluconazole (100 mg daily for 4 days) and triazolam (0.25 mg) the AUC and half-life of triazolam increased respectively 2.5 and 1.8 times. Prolonged and enhanced effects from triazolam have been observed. The combination may require reduction in the dose of triazolam.

Calcium channel antagonists (CYP3A4-substrates):
Some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, nicardipine, amlodipine, and felodipine, are metabolised via CYP3A4. Literature reports have documented substantial peripheral oedema and/or elevated calcium antagonist serum concentrations during concurrent use of itraconazole and felodipine, isradipine, or nifedipine. An interaction might occur also with fluconazole.

Carbamazepine (CYP3A4-substrate):
Carbamazepine is metabolized by isozyme CYP3A4. Fluconazole is thus likely to cause carbamazepine toxicity, probably due to inhibition of isozyme CYP3A4.

Celecoxib (CYP2C9-substrate):
In concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg), Cmax and AUC for celecoxib increased by 68 % and 134 % respectively.
Halving the dose of celecoxib is recommended in combination therapy with fluconazole.

Ciclosporin (CYP3A4-substrate):
Clinically significant interactions between ciclosporin and fluconazole have been observed at doses of fluconazole of 200 mg and higher. In concomitant treatment with 200 mg fluconazole daily and ciclosporin (2.7 mg/kg/day), AUC for ciclosporin increased approximately 1.8 times and clearance was reduced by approximately 55 %. The plasma concentration of ciclosporin should be monitored in concomitant treatment with fluconazole.
However, in another multiple dose study with 100mg daily, fluconazole did not affect ciclosporin levels in patients with bone marrow transplants. Ciclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.

Didanosine:
Coadministration of didanosine and fluconazole appears to be safe and has little effect on didanosine pharmacokinetics or efficacy. However, it is important to monitor fluconazole response. It may be advantageous to stagger fluconazole dosing to a time prior to didanosine administration.

Halofantrin (CYP3A4-substrate):
Drugs which inhibit CYP3A4 lead to an inhibition of halofantrin metabolism.

HMG-CoA-reductase-inhibitors (CYP2C9- or CYP3A4-substrate):
The risk of myopathy increases when fluconazole is administered concomitantly with HMG-CoA-reductase inhibitors that are metabolised via CYP3A4, e.g. atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. For fluvastatin an individual increase of up to 200% in the area under the curve (AUC) can occur as a result of interaction between fluvastatin and fluconazole. An individual patient using fluvastatin 80 mg daily may be exposed to considerable fluvastatin concentrations if treated with high doses of fluconazole. Caution should be observed where concomitant treatment with fluconazole and HMG-CoA-reductase-inhibitors is considered necessary.
The combination may require dose reduction of the HMG-CoA reductase inhibitors. The patient should be observed with regard to signs of myopathy or rhabdomyolysis and creatine kinase concentrations (CK). The HMG-CoA treatment should be stopped if CK concentrations show a marked increase or if myopathy or rhabdomyolysis is diagnosed or suspected.

Losartan (CYP2C9-substrate):
Fluconazole inhibits the conversion of losartan to its active metabolite (E-3174), which is responsible for the most of the angiotensin II receptor antagonism that occurs with losartan therapy. 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:
There are reports of a reinforced impact of methadone after concomitant administration of fluconazole and methadone. A pharmacokinetics study showed increased AUC of methadone (35% on average).

Oral contraceptive agents (CYP3A4-substrate):
In a kinetic study with combined oral contraceptives and 50 mg fluconazole daily, hormonal levels were not affected. With 200 mg fluconazole daily, AUC for ethynylestradiol increased by 40 % and levonorgestrel by 24 %.
In a 300 mg daily fluconazole study, the AUCs of ethinyl estradiol and norethindrone were increased by 24% and 13% 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):
Concomitant, repeated treatment with 200 mg fluconazole and 250 mg phenytoin intravenously increased AUC24 for phenytoin by 75 % and Cmin by 128 %. In combination treatment, plasma phenytoin concentrations should be monitored and the dose adjusted.

Prednisone (CYP3A4-substrate):
A liver transplant recipient receiving prednisone experienced an Addisonian crisis when a three-month course of fluconazole was discontinued. The withdrawal of fluconazole likely caused 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):
In concomitant treatment with fluconazole and rifabutin, the serum concentrations of rifabutin increased. Uveitis has been reported. Patients undergoing concomitant treatment should be monitored closely.

Sirolimus and tacrolimus (3A4-substrate):
In concomitant oral treatment with fluconazole and tacrolimus (0.15 mg/kg twice daily) the plasma concentration trough level of tacrolimus increased 1.4 and 3.1 times with a daily fluconazole dose of 100 mg and 200 mg respectively. Nephrotoxicity has been reported. Even though no interaction studies have been performed with fluconazole and sirolimus, a similar interaction can be anticipated. In concomitant treatment with fluconazole and tacrolimus or sirolimus, patients should be closely monitored and an adjustment in dose considered.

Sulphonylureas (CYP2C9-substrate):
Fluconazole has displayed prolonged half-life in serum for concomitantly administered sulphonylureas (glibencamide, glipizide, chlorpropamide and tolbutamide) in healthy volunteers.

Fluconazole may be administered to diabetics together with sulphonylureas, but the risk of hypoglycemia should be considered. Blood glucose levels should be closely monitored.

Theophylline:
In a placebo-controlled interaction study, the administration of fluconazole 200mg for 14 days resulted in an 18% decrease in the mean plasma clearance of theophylline. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and the therapy modified appropriately if signs of toxicity develop.

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 (bone marrow suppression, renal and hepatic dysfunction, and gastro-intestinal ulceration) must be closely monitored.

Xanthine bases, other antiepileptic drugs and isoniazid:
Follow-up tests must be carried out when fluconazol is administered concomitantly with xanthine bases, other antiepileptic drugs and isoniazide.

Zidovudine:
Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200mg daily for 15 days. There was a significant increase in zidovudine AUC (20%).
A second randomised, two-period, two-treatment crossover study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200mg every eight hours either with or without fluconazole 400mg daily for seven days. The AUC of zidovudine significantly increased (74%) during coadministration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

Interaction studies show that concomitant administration of Fluconazole with food intake, cimetidine, antacid, or following total body irradiation in bone marrow transplantation, does not significantly affect Fluconazole absorption.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but that such interactions may occur.

4.6 Pregnancy and lactation

Pregnancy
Data from several hundred pregnant women treated with standard doses of fluconazole (less than 200 mg/day) as a single or repeated dose during the first trimester of pregnancy, does not indicate undesirable effects on the foetus.
There are reports on multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in children whose mothers were treated for coccidiomycosis with high dose fluconazole (400-800 mg/day), for 3 months or longer. The relation between the use of fluconazole and these effects is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3), but the potential risk in humans is unknown.
Fluconazole in standard doses and short-term treatment should not be used during pregnancy unless clearly necessary.
Fluconazole in high doses or in prolonged regimens should not be used during pregnancy except for life threatening infections.

Lactation
Fluconazole passes into breast milk in concentrations lower than those in plasma.

Breast-feeding may be maintained after a single dose of fluconazole of 200 mg or less. Breast-feeding is not recommended after repeated use of after high-dose fluconazole.

4.7 Effects on ability to drive and use machines

Fluconazole 2mg/ml Solution for Infusion has negligible influence on the ability to drive and use machines. However, it should be borne in mind that dizziness and seizures may occur.

4.8 Undesirable effects

Side-effects associated with fluconazole observed in clinical trials and post-marketing studies are listed below. Frequencies are defined as 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Classes	Very Common ≥1/10	Common ≥1/100, <1/10	Un-common ≥1/1,000, <1/100	Rare ≥1/10,000, <1/1,000	Very Rare <1/10,000	Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders			Anaemia	Agranulocytosis, Luukopenia, neutropenia, thrombocyto-penia		
Immune System Disorders				Anaphylactic reactions, itching	Angio-edema face oedema	Urticaria
Psychiatric disorders			Insomnia, Somnol-ence			
Nervous System disorders		Headache	Convulsions, Seizures, Dizziness, paresthesia, taste perversion, tremor, vertigo			
Metabolism and nutrition disorders				Hypercholesterolemia, hypertriglycer-idemia, hypokalaemia		
Cardiac Disorders				Ventricular arrhythmia (QT prolongation, Torsade de Pointes)		
Gastrointestinal Disorders		Nausea, Vomiting, abdominal pain and diarrhoea	Dyspepsia, flatulence, anorexia, constipa-tion, dry mouth.			

Renal and Urinary disorders			Changes in renal function tests			
Hepatobi-liary disorders		Elevated alkaline phosphate-ase ASAT and ALAT	Cholestasis, Hepato-cellular damage, Jaundice, clinically significant increase of total bilirubin	Hepatic toxicity, hepatic necrosis, hepatic failure, hepatitis, heptocellular necrosis		
Skin and Subcutaneous tissue disorders		(maculopapular - erythema) rash	Urticaria, pruritis, sweating	Alopecia, exfoliative skin disorders (Stevens-Johnson syndrome)	Exfoliative skin disorders (toxic epidermal necroly-sis or Lyell syndrome	Urticaria, acute generalized exanthematous pustulosis, (fixed drug eruption
Musculo-skeleta 1 and connective tissue disorders			Myalgia			
General disorders and administration site conditions			Fatigue , malaise, asthenia, fever			

Adverse clinical events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

Paediatric patients:

Adverse events have been reported with a greater frequency in children as compared to all patients. Moreover, irritability and anaemia have been reported as specific for children.

4.9 Overdose

In most patients overdosing results in gastrointestinal complaints and skin reactions (itch, rash, etc.). There has been a report of an overdose with Fluconazole where a 42 year old HIV infected patient developed hallucinations and exhibited paranoid behavior after reportedly ingesting 8,200 mg of Fluconazole without medical supervision. The patient was admitted to the hospital, and his symptoms resolved within 48 hours.

In the event of overdosage, supportive measures and symptomatic treatment, and gastric lavage if necessary, may be adequate.

As Fluconazole is largely excreted in the urine, forced diuresis would probably increase the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Messer et al, 2006: SENTRY Antimicrobial Surveillance Program (2003)

Rex JH, 2000: IDSA Practice Guidelines for the Treatment of Candidiasis]

The antifungal spectrum of fluconazole includes a number of pathogens including *Candida albicans*, and non-*Candida albicans* species, *Cryptococcus* species and other dermatophytes.

The prevalence of acquired resistance may vary for some species geographically and with time. Therefore it is desirable to obtain information on local resistance patterns, particularly in the light of the adequate treatment of severe infections.

Interpretive breakpoints for *Candida* species:

Classification	MIC (microgrammes/ml)	Species	Data source
Sensitive (S)	NMT 8	*C. albicans,* *C. parapsilosis,* *C. lusitaniae* *C. kefyr,* *C. dubliniensis* *C. pelliculosa*	Pfaller MA et al, 2006 Messer SA et al, 2006 Rex JH, 2000
Susceptibility depends on the dose (S-DD)	16-32	*C. glabrata* (approx 17% R) *C. guillermondii* (approx 10% R) *C. famata* (approx 12% R) *C.tropicalis* (approx 4% R)	Pfaller MA et al, 2006 Messer SA et al, 2006 Rex JH, 2000
Resistant (R)	Greater than 32	*C. krusei,* *C. rugosa,* *C. inconspicua,* *C. norvegensis,* *C. lipolytica,* *C. zeylanoides.*	Pfaller MA et al, 2006 Messer SA et al, 2006 Rex JH, 2000

There are reports of resistant isolates of *Candida albicans* arising in AIDS patients who have received long-term treatment with fluconazole.
Cryptococcus neoformans is predominantly sensitive to fluconazole. Strains with an MIC value of greater than 32 microgrammes per ml are considered resistant.
Infections resulting from *Aspergillus* species, *Zygomycetes* including *Mucor* and *Rhizopus, Microsporum* and *Trichophyton* species should not be treated with fluconazole since fluconazole has little or no activity against these fungi.

5.2 Pharmacokinetic properties

Absorption:

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route.

Fluconazole is well absorbed after oral intake. The absolute bioavailability is above 90%. Oral absorption is not affected by concomitant food intake. The maximum fasting plasma concentration is reached 0.5-1.5 hours after dose intake. 90% of the steady-state level is reached 4-5 days after dosing once daily.

Plasma concentration is proportional to the dose. After administration of 200 mg of fluconazole, C_{max} 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, C_{max} is around 9 mg/l and plasma concentrations at steady-state after 15 days are around 18 mg/l. Intake of a double dose on Day 1 results in plasma concentrations of approximately 90% of steady-state on Day 2.

Distribution:

The apparent volume of distribution of fluconazole corresponds to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis the fluconazole levels in the CSF are about 80% of the corresponding plasma levels.

In the stratum corneum, epidermis-dermis and exocrine sweat higher concentrations of fluconazole are reached compared with those in serum. Fluconazole accumulates in the stratum corneum. For example, at a dose of 150 mg once weekly, the concentration of fluconazole in stratum corneum after two doses was 23.3 microgrammes/g and seven days after the end of treatment it was still 7.1 microgrammes/g.

Biotransformation:

Breakdown of fluconazole is modest. Only 11% of a radioactive dose is excreted in the urine as metabolites.

Elimination:

The major route of excretion is renal. Approximately 80% of the dose excreted in the urine in the non-metabolised form. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

The average plasma half-life is about 30 hours. The long plasma half-life provides the basis for treatment with single daily doses in all indications.

Pharmacokinetics in children:

Children eliminate fluconazole more rapidly than adults do.

In children (after the neonatal phase) and adolescents of 5-15 years of age the plasma half-life is between 15.2 - 17.6.

Premature babies have a shorter plasma half-life (about 70 hours) and a larger volume of distribution (1.2-2.3 litres/kg) than babies born at full term. During the first week after birth and in the course of the neonatal period, plasma Fluconazole clearance rises (and the plasma half-life falls).

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

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 SPC.
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

Water for injections,
Sodium chloride,
Hydrochloric acid (for pH adjustment),
Sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf Life

5 years (25 ml, 50 ml, 100 ml and 200 ml)

After first opening:
From the microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

Clear type 1 glass bottle, closed with a bromobutyl rubber stopper and aluminum cap.

Pack size:
1 x 25ml, 1 x 50ml, 1 x 100ml and 1 x 200ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

The product should be inspected visually for particles and discoloration prior to administration. Only clear and colourless solution should be used.

Fluconazole 2mg/ml solution for infusion is compatible with the following infusion fluids:
a. glucose 20% when available
b. Ringer's solution when available
c. Hartmann's solution when available
d. Potassium chloride in glucose when available
e. sodium carbonate 4.2% when available
f. 0.9% sodium chloride (isotonic saline) when available
Compatibility has only been shown for short duration (10 minutes).
Dilution of Fluconazole 2mg/ml solution for infusion is not required prior to administration. If necessary, Fluconazole and the solutions mentioned above should be administered through separate infusion containers. The two reservoirs should be connected using a "Y" connection. The two solutions are then mixed in a single line and the administration is performed. The above method is recommended in order to avoid effects such as the "layering effect" if the two solutions were mixed in one infusion container for the total period of the administration.

7 MARKETING AUTHORISATION HOLDER

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