Public Assessment Report
Decentralised Procedure

Fluconazole 2mg/ml Solution for Infusion
Fluconazole

UK/H/1089/01/DC

UK licence no: PL 24598/0011

Noridem Enterprises Limited
LAY SUMMARY

On 4th November 2009, the UK granted Noridem Enterprises Limited a marketing Authorisation (licence) for the medicinal product Fluconazole 2mg/ml Solution for Infusion. This is a prescription-only medicine (POM) that is used for the treatment of fungal disorders caused by yeast and fungi.

Fluconazole belongs to the triazole derivative class of drugs. Fluconazole is type of medicines called an antifungal agent. Antifungal agents work by treating infections caused by fungi or yeasts. They can also stop you getting a fungal infection.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Fluconazole 2mg/ml Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.
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Module 6  Steps taken after initial procedure
## Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Fluconazole 2mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10.1</td>
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<tr>
<td>Active Substance</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Form</td>
<td>Solution for Infusion</td>
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<tr>
<td>Strength</td>
<td>2mg/ml</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Noridem Enterprises Ltd, Evagorou &amp; Makariou, Mitsi Building 3, Suit.115, 1065 Nicosia, Cyprus</td>
</tr>
<tr>
<td>RMS</td>
<td>UK</td>
</tr>
<tr>
<td>CMS</td>
<td>AT, FR, DE, EL, IE, ES</td>
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<td>Procedure Number</td>
<td>UK/H/1089/01/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210: 5th October 2009</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Fluconazole 2mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One ml of solution for infusion contains 2 mg of fluconazole.

Each 50ml bag contains 100mg of fluconazole.

Each 100ml bag contains 200mg of fluconazole.

Excipients:
Sodium, 3.54 mg/ml
Each 50 ml bag contains 177 mg (7.7 mmol) sodium.
Each 100 ml bag contains 354 mg (15.4 mmol) sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for infusion.

Clear, colourless, sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Adults

Treatment of mycoses caused by Candida, Cryptococcus 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;
prophylaxis against deep Candida infections (especially Candida albicans) in patients with neutropenia due to bone marrow transplant.

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

In some patients with severe cryptococcal meningitis the mycological response during fluconazole treatment may be slower than during 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.
Fluconazole should not be used for tinea capitis.

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

Method of administration

Only for intravenous use as infusion.

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 the 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 treatment. The patient should be switched from intravenous to oral administration 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.

THE ELDERLY
The normal adult dose should be given if there is no evidence of renal impairment. Please refer to Table 1.

Table 1 – Guidelines for the dose to be administered to adults who are treated intravenously

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initial daily dose (mg)</th>
<th>Subsequent daily dose (mg)</th>
<th>Recommended duration of treatment</th>
<th>Additional recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic candidiasis: candidaemia, disseminated candidiasis and other forms of invasive candidal infection</td>
<td>400-800</td>
<td>200-400</td>
<td>dependent on the clinical response</td>
<td>The dose chosen must take into account local patterns of resistance to fluconazole (see 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 800 mg on the first day, followed by 400 mg daily thereafter may be preferable. Use only when oral administration is not possible. In some cases a daily dose higher than 100 mg may be required and treatment can be prolonged. The duration of maintenance treatment of AIDS patients should be weighed against the increased risk of resistance to fluconazole.</td>
</tr>
<tr>
<td>Severe mucosal candidiasis: oropharyngeal candidiasis</td>
<td>100</td>
<td>100</td>
<td>7 to 14 days</td>
<td></td>
</tr>
<tr>
<td>other mucosal Candida infections (except genital candidiasis)</td>
<td>100</td>
<td>100</td>
<td>14 to 30 days</td>
<td></td>
</tr>
<tr>
<td>Treatment of cryptococcal meningitis: initial treatment</td>
<td>400</td>
<td>200-400</td>
<td>Typically 6 to 8 weeks</td>
<td>The duration of treatment depend on the clinical and mycological response.</td>
</tr>
<tr>
<td>Prophylaxis against deep Candida infections: in patients with neutropenia due to bone marrow transplantation</td>
<td>400</td>
<td>400</td>
<td>See additional guidance</td>
<td>Fluconazole administration should start several days before the expected onset of neutropenia, and continue for seven days after the neutrophil count rises above 1000 cells per mm³.</td>
</tr>
</tbody>
</table>
PAEDIATRIC USE

Fluconazole 2mg/ml is not recommended for use in children and adolescents under the age of 16 years due to insufficient data on safety and efficacy (see section 5.2).

It may only be used if there is no therapeutic alternative available. Please refer to Table 2 for specific dosage recommendations.

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

For children with impaired renal function, see dosing in “Use in patients with impaired renal function”

Table 2 – Guidance on the dose to be administered in paediatric patients treated by the intravenous route

<table>
<thead>
<tr>
<th>Age group</th>
<th>Indication(s)</th>
<th>Recommended dosage</th>
<th>Additional recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>Note: There are few pharmacokinetic data supporting the posologies in newborn babies (see section 5.2).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks or less</td>
<td>all indications listed below</td>
<td>6 – 12 mg/kg every 72 hours</td>
<td>A maximum dose of 12 mg/kg every 72 h should not be exceeded in children in the first two weeks of life. In children between 3 and 4 weeks of life, 12 mg/kg every 48 h should not be exceeded.</td>
</tr>
<tr>
<td>3 to 4 weeks</td>
<td>all indications listed below</td>
<td>6 – 12 mg/kg every 48 hours</td>
<td></td>
</tr>
<tr>
<td>Children of four weeks and older</td>
<td>Note: A maximum dose of 400mg daily should not be exceeded in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>systemic candidiasis</td>
<td>6 – 12 mg/kg per day</td>
<td>On the first day a loading dose of 6 mg/kg may be given in order to more rapidly reach the steady state. The dose should be dependent on the extent and duration of the induced neutropenia (see adult dosing)</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mucosal candidiasis</td>
<td>3 mg/kg per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fungal infection prevention in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy</td>
<td>3-12 mg/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

PATIENTS (ADULT AND PAEDIATRIC) WITH IMPAIRED RENAL FUNCTION

Fluconazole cleared primarily by renal excretion as unchanged drug.

In patients with impaired renal function who receive multiple dose therapy, the recommended initial loading dose can be given (see Table 1). After the loading dose, the daily dose (according to indication) is adjusted in relation to creatinine clearance as follows:

Table 3 – Required dose adjustments after the initial dose for patients with impaired renal function
(Depending on the clinical condition, extra adjustments of the dose may be required.)

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/minute)</th>
<th>Percentage of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>normal dosage regimen (100%)</td>
</tr>
</tbody>
</table>
The pharmacokinetics of fluconazole has not been studied in children with renal insufficiency.

Patients with hepatic 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.

Infusion rates and instructions for use

The infusion rate should not exceed 10 ml/min (20 mg/min) for adults.

In children the rate of intravenous infusion should not exceed 5 ml/min (10 mg/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 is formulated in 0.9% sodium chloride solution; each 100ml of the solution for infusion 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 choice of the appropriate route of administration 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 which are metabolised by CYP3A4, such as cisapride, astemizole, terfenadine, pimozide and quinidine. See section 4.4 and section 4.5.

4.4 Special Warnings and precautions for use:

There is some evidence that in some patients with cryptococcal meningitis the mycological response during fluconazole treatment may be slower compared to treatment with amphotericine B in combination with flucytosine. This should be taken into account for the treatment choice in patients with severe cryptococcal meningitis.

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.

Because a causal relationship with fluconazole cannot be excluded, patients who develop abnormal liver function tests during fluconazole therapy should be monitored for signs of the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment.

Severe hepatic toxicity, including death, has been reported in rare cases, most often in patients with serious underlying diseases. No obvious relationship between hepatotoxicity and total daily dose of fluconazole, duration of therapy, gender or age of the patient has been observed.
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 50ml/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
- clinically significant (including sinus) bradycardia
- symptomatic arrhythmias
- Electrolyte disturbances
- Concomitant administration of medicinal products 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 during 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 extend 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 exercised in patients with renal impairment. Please refer to 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).

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.

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

This medicinal product contains 15.4mmol (354mg) sodium per 100 ml of solution. This should 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.

After administration of fluconazole, the following interactions have been reported.

The following combinations are contraindicated (see section 4.3):

Astemizole (CYP3A4 substrate):
Astemizole overdoses have led to prolonged QT interval, severe ventricular arrhythmia, torsades 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):
In patients who were administered fluconazole and cisapride simultaneously, cases of heart disorders have been reported, including torsades de pointes. Cardiovascular effects, including torsade de pointes, have been reported in patients having received concomitant treatment with fluconazole and cisapride. Administration of 200mg fluconazole once daily concomitantly with cisapride 20mg four times daily, led to a significant increase in plasma levels of cisapride and prolongation of the QTc-interval. Concurrent treatment with fluconazole and cisapride is contraindicated (see section 4.3).

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

The effects of other drugs on fluconazole

Hydrochlorothiazide:
In a pharmacokinetic interaction study with healthy volunteers who concomitantly received fluconazole and multiple doses of hydrochlorothiazide the plasma concentrations of the fluconazole increased by 40%. Even though an effect of this size should not give rise to any need to change the fluconazole dose in patients who are concomitantly treated with diuretics, the prescriber should be aware of this.

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

Possible effects of fluconazole on the metabolism of other drugs

Alfentanil (CYP3A4 substrate):
On simultaneous intravenous administration of 400mg fluconazole and 20 microgram/kg alfentanil to healthy volunteers, the AUC of alfentanil increased twofold and clearance decreased by 55%, probably through inhibition of CYP3A4. The combination may require dose adjustment.

Amitriptyline:
Several case reports have described the development of elevated amitriptyline concentrations and signs of tricyclic toxicity when amitriptyline is used in combination with fluconazole. Concomitant infusion of fluconazole and nortriptyline, the active metabolite of amitriptyline, has been reported to lead to increased nortriptyline levels. Due to the risk of amitriptyline toxicity, monitoring of amitriptyline 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.

Antiretroviral drugs (CYP3A4 substrate):
There are reports of increased serum levels following concurrent administration of fluconazole with antiretroviral agents such as nevirapine.

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 (400mg) and midazolam (7.5mg) 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 (100mg daily for 4 days) and triazolam (0.25mg) 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 antagonists (CYP3A4 substrate):
Some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, nicardipine, amlodipine, and felodipine, are metabolised via CYP3A4. There are reports of extensive peripheral oedema, vertigo, hypotension, headache, redness of the face and/or elevated serum calcium antagonist concentrations arising following co-administration of theazole itraconazole with felodipine, isradipine or nifedipine. An interaction might occur also with fluconazole.

Carbamazepine (CYP3A4 substrate):
There are reports of increased serum carbamazepine levels following concurrent administration of fluconazole and carbamazepine.

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

Ciclosporin (CYP3A4 substrate):
In concomitant treatment with 200 mg fluconazole daily and ciclosporin (2.7mg/kg/day), AUC for ciclosporin increased approximately 1.8 times and clearance was reduced by approximately 55%. However, in another multiple dose study with 100mg daily, fluconazole did not affect ciclosporin levels in patients with bone marrow transplants. The plasma concentration of ciclosporin should be monitored in concomitant treatment with fluconazole.

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 the fluconazole response. It may be advantageous to stagger fluconazole dosing to a time prior to didanosine administration.

Halofantrine (CYP3A4 substrate):
Drugs that inhibit CYP3A4 lead to inhibition of halofantrine metabolism and can cause a prolongation of the QT interval. The concomitant use of fluconazole and halofantrine is not recommended.

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 metabolized via CYP3A4 e.g. atorvastatin or simvastatin, or by 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. Patients should be observed with regard to signs of myopathy or rhabdomyolysis and creatine kinase levels (CK). The HMG-CoA treatment 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 conversion of losartan to its active metabolite (E-3174), which is responsible for most of the angiotensin II receptor antagonism that occurs with losartan therapy. Simultaneous treatment with fluconazole may lead to increased losartan concentrations and decreased concentrations.
of the active metabolite. It is recommended that patients receiving the combination be monitored for continued control of their hypertension.

**Methadone (CYP3A4 substrate):**
There have been reports of an intensified effect of methadone after simultaneous administration of fluconazole and methadone. One pharmacokinetic study showed an average increase in the AUC of methadone by 35%.

**Oral contraceptives:**
Two pharmacokinetic studies have been carried out with combined oral contraceptives and repeated doses of fluconazole. There were no relevant effects on either hormone level when 50 mg fluconazole was administered. Fluconazole given 200 mg daily raised the AUC of ethinylestradiol and levonorgestrel by 40% and 24% respectively. Multiple dose use of fluconazole is therefore unlikely to influence the effect of the combined oral contraceptive.

**Phenytoin (CYP2C9 substrate):**
With intravenous administration of 200 mg fluconazole together with 250 mg phenytoin, the AUC and the Cmin of phenytoin increased by 75% and 128%, respectively. In combination treatment, plasma phenytoin concentrations should be monitored and the dose adjusted.

**Prednisone (CYP3A4 substrate that is metabolised to prednisolone):**
A liver transplant recipient receiving prednisone experienced an Addisonian crisis when a three-month course of fluconazole was discontinued. Withdrawal of fluconazole probably caused an increase in CYP3A4 activity, so that degradation of prednisone increased. Patients undergoing long-term treatment with fluconazole and prednisone (or other adrenocorticoid therapy) should be closely monitored for signs of adrenal insufficiency when fluconazole is discontinued.

**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.

**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.

**Tacrolimus and sirolimus (CYP3A4 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.

**Theophylline:**
Administration of 200 mg fluconazole for 14 days led to 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 isoniazide:**
Follow-up tests must be carried out when fluconazole is administered concomitantly with xanthine bases, other antiepileptic drugs and isoniazide.

Zidovudine:
Interaction studies have shown that when zidovudine is taken together with fluconazole 200 mg or 400 mg daily the zidovudine AUC values may be raised by between 20% and 70%, probably as a result of the inhibition of conversion to the glucuronide. Patients receiving this combination should be monitored for zidovudine-related adverse reactions.

Other interactions with medicinal products

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 its membrane permeability. The clinical effect of this antagonism is still unknown, and a similar effect may occur with the amphotericin B cholesterol sulfate complex.

Drugs that cause QT prolongation:
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 the QT interval should be carefully monitored since an additive effect cannot be excluded.

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 200mg/day) administered 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, ear dysplasia, giant anterior fontanelle, femoral bowing and radioulnar synostosis) in children whose mothers were treated for coccidioidomycosis with high dose fluconazole (400 – 800mg/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 at high doses or in prolonged regimens should not be used during pregnancy except for life threatening infections.

Due to potential teratogenic effects women of childbearing potential must use effective contraception during treatment.

Lactation

Fluconazole is secreted into breast milk at concentrations lower than those in plasma. Breast-feeding may be continued after a single dose of 200mg fluconazole or less. Breast-feeding is not recommended after repeated use or 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, seizures and other side effects may occur (see section 4.8).

4.8 Undesirable effects

Adverse reactions 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.

Adverse reactions with very common (≥1/10) frequency until now have not been recognized.

<table>
<thead>
<tr>
<th>System Organ Classes</th>
<th>Common (≥1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
<th>Very rare (&lt; 1/10,000), Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection and infestation</td>
<td></td>
<td>anaemia</td>
<td>agranulocytosis, leukopenia, neutropenia, thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>anaphylactic reactions</td>
<td>angioedema, face oedema</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>hypercholesterolemia, hypertriglyceridemia, hypokalaemia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>headache</td>
<td>convulsions, dizziness, paraesthesiae, abnormal taste sensations, tremor, vertigo</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td>ventricular arrhythmia (QT prolongation, Torsade de Pointes) (see section 4.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>vomiting, nausea, abdominal pain, diarrhea</td>
<td>dyspepsia, flatulence, anorexia, constipation, dry mouth,</td>
<td>hepatitis, liver cell necrosis, liver failure with isolated fatalities. The appropriate laboratory values should be very closely monitored (see section 4.4)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>increase in the serum activities of liver-derived enzymes such as ALP, ALT and AST</td>
<td>cholestasis, a clinically relevant rise in total bilirubin, jaundice, hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>maculopapular erythema, rash</td>
<td>urticaria, pruritus increased sweating</td>
<td>exfoliative skin disorders (Stevens-Johnson syndrome, alopecia) exfoliative skin disorders (toxic epidermal necrolysis or Lyell syndrome) acute generalized exanthematous pustulosis, (fixed) drug eruption</td>
</tr>
<tr>
<td>Musculoskeletal,</td>
<td></td>
<td>myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>connective tissue and bone disorders</td>
<td>Renal and urinary disorders</td>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>changes in renal function tests</td>
<td>fatigue, malaise, asthenia, fever</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

4.9 **Overdose**
In most patients overdose 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.

**Treatment**
In the event of overdose, supportive measures and symptomatic treatment, and gastric lavage if necessary, may be adequate.
Fluconazole is mainly excreted in the urine. A 3-hour haemodialysis session reduces plasma levels by approximately 50%. No data are available on the effect of forced diuresis.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic category
Antimycotics for systemic use, triazole derivatives.
ATC code: J02A C01.

**Mechanism of action**
Fluconazole belongs to the triazole class of antimycotics, with a mainly fungistatic action. It is a potent and selective inhibitor of ergosterol synthesis in fungi, which leads to defects in the cell membrane. Fluconazole is very specific for fungal cytochrome P450 enzymes.

**Mechanism of resistance**
Depending on the yeast species involved, the principal mechanisms of resistance to fluconazole, in common with other azole antifungal agents, involve impairing the accumulation of the drug in the cell by

(i) altering the amino acid composition of lanosterol 14α-demethylase,
(ii) increasing drug efflux, and
(iii) altering the ergosterol biosynthetic pathways.

In Candida albicans, blockage of the ergosterol synthetic pathways is thought to primarily arise from blockage of sterol C5,6-desaturase which is encoded by ERG3. In the more resistant species, Candida glabrata, the predominant pathway has not been fully elucidated but is thought to arise from upregulation of CDR genes (CDR1, CDR2 and MMDR1) responsible for efflux of the drug substance from the cells. Resistance to fluconazole therefore usually confers resistance to other azole antifungal agents. In Cryptococcus neoformans the studies have demonstrated that the same principle mechanisms of resistance exist in this species, and that these may be affected by prior exposure to azole antifungal agents.

Similar careful consideration of the benefits of the proposed dose versus the risk of development of resistance must therefore be applied with fluconazole as for any other antimicrobial chemotherapy.
Breakpoints
According to EUCAST, the following clinical breakpoints apply for fluconazole:

<table>
<thead>
<tr>
<th>Organism</th>
<th>EUCAST Breakpoints (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
</tr>
<tr>
<td>Candida albicans, Candida</td>
<td>2</td>
</tr>
<tr>
<td>parapsilosis, Candida tropicalis</td>
<td>4</td>
</tr>
<tr>
<td>Non-species related breakpoints</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

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

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.albicans</td>
</tr>
<tr>
<td>C.kefyr</td>
</tr>
<tr>
<td>C.lusitaniae,</td>
</tr>
<tr>
<td>C.parapsilosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.dubliniensis</td>
</tr>
<tr>
<td>C.famata</td>
</tr>
<tr>
<td>C.guillermondii</td>
</tr>
<tr>
<td>C.pelliculosa</td>
</tr>
<tr>
<td>C.tropicalis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inherently resistant organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.glabrata</td>
</tr>
<tr>
<td>C.krusei</td>
</tr>
</tbody>
</table>

Resistant isolates of Candida albicans have been found in AIDS patients who have undergone long-term treatment with fluconazole.

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.

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 6mg/kg/day for 6 weeks was not superior to griseofulvin administered at 11mg/kg/day for 6 weeks. The overall success rate at 6 weeks was low (fluconazole 6 weeks: 18.3%; fluconazole 3 weeks: 14.7%; griseofulvin: 17.7%) across all the treatment groups. These findings are not inconsistent with the natural history of tinea capitis without therapy.

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 greater than 90%. Oral absorption is not affected by simultaneous food intake. The maximum fasting plasma concentration is reached 0.5-1.5 h after administration of the dose. 90% of the steady-state level is reached 4-5 days after dosing once daily.

The plasma concentration is proportional to the dose. After administration of 200mg fluconazole, C_max is approx. 4.6mg/l and the plasma steady-state concentrations after 15days are about 10mg/l. After
administration of 400mg fluconazole, Cmax is approx. 9mg/l and the plasma steady-state concentrations after 15 days are about 18mg/l. Taking a double dose on day 1 leads to plasma concentrations of approx. 90% of the plasma steady-state concentrations on day 2.

Distribution
The apparent volume of distribution of fluconazole corresponds to total body water. Binding to plasma proteins is low (11% - 12%).

Fluconazole achieves good penetration into all body fluids studied. The fluconazole concentrations in saliva and sputum are comparable to the plasma concentrations. In patients with fungal meningitis the fluconazole concentrations in cerebrospinal fluid (CSF) are approx. 80% of the corresponding plasma concentrations.

In the stratum corneum, the epidermis-dermis and exocrine sweat, higher fluconazole concentrations are reached than in serum. Fluconazole accumulates in the stratum corneum. With a once weekly dose of 150 mg, for example, the fluconazole concentration in the stratum corneum after two doses was 23.3 micrograms/g. Seven days after the end of the treatment the fluconazole concentration was still 7.1 micrograms/g.

Biotransformation
Fluconazole is broken down to a modest extent. Only 11% of a radioactive dose is excreted in the form of metabolites in the urine.

Elimination
Fluconazole is mainly excreted via the kidneys. Approximately 80% of the dose is excreted in non-metabolized form in the urine. Fluconazole clearance is proportional to the creatinine clearance. There is no evidence of circulating metabolites. The mean half-life in the plasma is approx. 30 h. The long plasma half-life provides the basis for treatment with single daily doses in all indications.

Pharmacokinetic properties 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 – 8mg/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 880ml/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 950ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature new-borns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9Kg (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 6mg/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.

The pharmacokinetic properties of fluconazole have not been investigated 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
Sodium chloride
Water for injections

6.2 Incompatibility
In absence of compatibility studies, this medicinal product must not be mixed with other medicinal product except those mentioned in section 4.2. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf-life
Unopened: 2 Years

After opening: From a microbiological point of view, the dilutions should be used immediately

Chemical and physical in-use stability after dilution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 36 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precaution for storage
Store below 25°C. Do not refrigerate or freeze. Keep the bag in the outer carton to protect from light.

For storage condition of diluted product see section 6.3

6.5 Nature and content of container
50 ml or 100 ml in plastic bags of polypropylene with rubber (type I) closures, and Aluminium caps with caps with plastic flip-top covers. Pack sizes of 10 bags.

6.6 Special precautions for disposal and other handling
For single use only. Discard any unused solution.

The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Fluconazole 2 mg/ml solution for infusion can be infused by means of an infusion system with one of the following solutions and should not be mixed with other medicinal products in a solution infusion.

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Resulting concentration of fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride injection 0.9%</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Dextrose injection 20%</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Lactated Ringer’s injection</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Ringer’s injection</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Potassium chloride 0.3%-Dextrose 5% injection</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Sodium Bicarbonate 4.2% injection</td>
<td>1.0 mg/ml</td>
</tr>
</tbody>
</table>

Any unused product or waste material should be disposed of in accordance with local requirements.
7. **MARKETING AUTHORISATION HOLDER**
   Noridem Enterprises Limited
   Evagoou & Makariou,
   Mitsi Building 3
   Suite 115,
   Nicosia, 1065
   Cyprus

8. **MARKETING AUTHORISATION NUMBER (S)**
   PL 24598/0011

9. **DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**
   4/11/2009

10. **DATE OF REVISION OF THE TEXT**
     04/11/2009
Module 3
Patient Information Leaflet

Fluconazole 2 mg/ml Solution for Infusion

Please read all of this leaflet carefully. It includes important information on how you should take this medicine correctly and safely.

• Keep this leaflet. You may need to read it again.
• If you are the parent of a child who is to be given this medicine, read the leaflet replacing “you” with “your child” throughout.
• The medicine is prescribed only for you, and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects get serious, or you notice any side effects not listed in the leaflet, please tell your doctor, nurse or pharmacist.
• If you have further questions, please ask your nurse, doctor or pharmacist.

The name of your medicine is Fluconazole 2mg/ml Solution for Infusion

In the rest of this leaflet Fluconazole 2mg/ml solution for infusion is called Fluconazole.

In this leaflet:
1. What Fluconazole is and what it is used for
2. Before you are given Fluconazole
3. How Fluconazole is given
4. Possible side-effects
5. How to store Fluconazole
6. Further information

1. What Fluconazole is and what it is used for

Fluconazole is type of medicine called an antifungal agent. Antifungal agents work by treating infections caused by fungi or yeasts. They can also stop you getting a fungal infection.

The most common cause of fungal infections is a yeast called Candida. Fluconazole may be used to treat some of the following infections caused by fungi or yeasts:

Adults
You may be given Fluconazole by your doctor to treat fungal infections such as:
• Internal (systemic) infections caused by Candida
• Severe infections of mucous membranes such as the upper airways, mouth, oesophagus and throat, caused by Candida, where oral treatment is not possible
• Meningitis caused by Cryptococcus

You may also be given Fluconazole to stop you from getting a fungal infection (if you’re going to have a bone marrow transplant) or to stop meningitis from coming back if you have had fungal meningitis and you have AIDS.

Children and adolescents
You may be given Fluconazole by your doctor to treat fungal infections such as:
• Internal (systemic) infections caused by Candida
• Severe infections of mucous membranes such as the upper airways, mouth, oesophagus and throat, caused by Candida, where oral treatment is not possible
2. **Before you take Fluconazole**

The doctor or nurse giving you this medicine will ask some questions about you. They need the following information before you have this medicine for the first time.

**Do not take Fluconazole**
- If you are allergic (hypersensitive) to fluconazole or any of the other ingredients in this medicine.
- If you are taking a medicine called cisapride, used to treat stomach upsets
- If you are taking a medicine called terfenadine, used to treat allergies.
- If you are taking a medicine called astemizole, used to treat allergies (may make the amount of astemizole in your blood too high)
- If you are taking a medicine called pimozide, used to treat schizophrenia
- If you are taking a medicine called quinidine, used to treat heart problems
- In children suffering from tine capitis (fungal infection of the skin)

**Do not take Fluconazole if any of the above statements are true.**

**Take special care with Fluconazole**

**Before your treatment starts, tell your doctor or nurse if:**
- You have AIDS or cancer
- You have meningitis
- You have kidney problems
- You have liver problems
- You have had serious skin reactions in the past such as blistering of the skin, mouth, eyes and genitals
- You have heart disease including heart rhythm problems
- You have abnormal levels of potassium, calcium or magnesium in your blood
- You are on a low sodium (salt) diet (see further information at the end of this section).

**During or after treatment make sure to tell your doctor or nurse immediately:**
- If you develop a rash, particularly if you are being treated for an internal infection.

**Taking other medicines**

Please tell your doctor about any medicines you may be taking or have recently been taking. Remember also any medicines you may be taking that do not need a prescription.

If you are taking any of the following medicines, it is very important to tell your doctor:

- Alfentanil, an anaesthetic drug used in surgery
- Amitriptyline, used to treat depression
- Amphotericin B, used to treat fungal infections
- Astemizole, used to treat allergies (may make the amount of astemizole in your blood too high)
- Carbamazepine, used to treat epilepsy
- Ciclosporin, used to help the immune system (may make the amount of ciclosporin in your blood too high)
- Cisapride, used to treat stomach upsets (may make the amount of cisapride in your blood too high)
- Didanosine, used to treat HIV and AIDS
- Halofantrine, used to treat malaria
- Hydrochlorothiazide, used to treat water retention and high blood pressure (may make the amount of Fluconazole in your blood too high)
- Isoniazid, used to treat tuberculosis
- Losartan, used to treat high blood pressure
- Methadone, used for pain relief
- Midazolam and other benzodiazepines which may be used as a sedative (may make the amount of midazolam in your blood too high)
- Nevirapine, used to treat HIV and AIDS
- Drugs such as niphedipine, used to treat high blood pressure
- Oral contraceptives “the pill”
- Phenytoin, used to treat epilepsy (may make the amount of phenytoin in your blood too high).
- Prednisone and other steroid medications used in a variety of conditions including asthma and joint disease
• Rifampicin, an antibiotic to treat tuberculosis (you may need to have a larger dose of fluconazole)
• Rifabutin, an antibiotic to treat tuberculosis (may make the amount of Rifabutin in your blood too high)
• Simvastatin, used to reduce the amount of cholesterol in your body
• Sulphonylureas such as chlorpropamide, glibenclamide, glipizide and tolbutamide used to control diabetes (Fluconazole can make the sulphonylurea stay in your blood too long)
• Tacrolimus, used to help the immune system (may make the amount of tacrolimus in your blood too high)
• Terfenadine, used to treat allergies (may make the amount of terfenadine in your blood too high)
• Theophylline, used to treat asthma (may make the amount of theophylline in your blood too high)
• Trimetrexate, used to treat pneumonia
• Warfarin, used to prevent blood clots (may affect how warfarin works and may cause side effects)
• Zidovudine (also called AZT), used to treat HIV patients (may make the amount of zidovudine in your blood too high).

Your doctor may want to carry out some extra blood tests if you are taking any of these medicines to check that your medicines are working together correctly.

Pregnancy and breastfeeding
• If you are pregnant, or think you may be pregnant you must tell your doctor
• If you are breastfeeding, you must tell your doctor as the Fluconazole will be in the breastmilk and may affect your baby.

Your doctor will not usually give you this medicine during pregnancy and breastfeeding.

Driving and using machines
It is unlikely that Fluconazole will affect your ability to drive or operate machines.

Important information about some of the ingredients of Fluconazole
Fluconazole contains salt (sodium chloride). The solution for infusion contains 3.54mg of sodium per ml.
One bag of 50ml contains 177mg of sodium.
One bag of 100ml contains 354mg of sodium.

This should be taken into consideration by patients on a controlled sodium diet.
If you are on a low sodium (salt) diet tell your doctor or other medical staff before they give you Fluconazole 2mg/ml solution for infusion.

3. How to take Fluconazole

A doctor or a nurse will usually give you this medicine.

Your doctor or nurse will give you the correct dose as a drip into your vein (your doctor or nurse may call this an IV or intravenous infusion). This may take between 30 and 60 minutes depending on the amount you are getting.

Your doctor will decide the amount (dose) of your medicine to give you. This will depend on a number of things. These things include how bad your infection is, the type of infection and the type of fungi or yeast causing it, your body weight, your age and how well your kidneys are working.

Adults and elderly (over 65 years old):
The usual dose for infections is provided below:

Mucosal infections of the mouth such as thrush
100mg once daily for 7 to 14 days.

Mucosal infections of the throat, upper respiratory tract or food pipe
100mg once daily for 14 to 30 days.

Internal fungal infections caused by Candida
400mg to 800mg on the first day followed by 200mg daily increased to a maximum of 400mg daily until your doctor thinks you are better.
To stop you from getting a fungal infection
400mg daily while you are at risk from an infection.

Children over 4 weeks old
The usual dose for infections is provided below:
- Mucosal infections: 3mg/kg bodyweight once daily
- Internal fungal infections caused by *Candida* or *Cryptococcus*: 6-12mg/kg bodyweight once daily.
- Fungal infection in children with low immune systems due to chemotherapy: 3-12 mg/kg bodyweight once daily.

Children 2 – 4 weeks old
- Mucosal infections: 6-12mg/kg bodyweight every 48 hours
- Internal fungal infections caused by *Candida* or *Cryptococcus*: 6-12mg/kg bodyweight every 48 hours.

Children less than 2 weeks old
- Mucosal infections: 6-12mg/kg bodyweight every 72 hours
- Internal fungal infections caused by *Candida* or *Cryptococcus*: 6-12mg/kg bodyweight every 72 hours.

Patients with kidney problems:
Your doctor may have to change your dose if you have problems with your kidneys.

If you receive more Fluconazole than you should
A doctor or a nurse will usually give you this medicine. If you think you may have received too much medicine, please tell your doctor or nurse at once.

If you miss a dose of Fluconazole
A doctor or a nurse will usually give you this medicine. If you think you have missed a dose, please tell your doctor or nurse.

If you stop taking Fluconazole
It is very important to finish the course of treatment your doctor has prescribed, even if you start to feel better. If you do not finish the course of treatment, your infection may get worse again.

If you have further questions on the use of your medicine, ask your doctor, nurse or pharmacist.

Please read the next page of this leaflet

4. Possible side-effects

Like all medicines, Fluconazole can cause side effects, although not everybody gets them.

These side effects may occur with certain frequencies, which are defined as follows:
- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: frequency cannot be estimated from the available data.

The following side effects are important and will require immediate action if you experience them. You should stop taking fluconazole and see your doctor immediately if the following symptoms occur:

Rare side effects
- a sudden allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- severe, extensive, blistering skin rash.

Very rare side effects
- swelling of the face, tongue and windpipe which can cause great difficulty in breathing.

The following side-effects have also been reported:
Common side effects
- headache
- skin rash
- feeling sick
- being sick (vomiting)
- stomach ache or pain
- diarrhoea
- alterations in the blood test results of liver function.

Uncommon side effects
- changes in how food tastes, dry mouth
- dizziness
- fits (convulsions)
- indigestion
- wind (flatulence)
- yellowing of the skin and eyes (jaundice) and liver abnormalities
- itching or rash, wheals, swelling or blistering (hives)
- increased sweating
- loss of appetite
- changes in blood test results of kidney function
- abnormal sleep
- numbness, trembling, dizziness
- pains in muscles
- feeling weak and tired
- fever
- anaemia

Rare side effects
- increased levels of fats in the blood (cholesterol and triglycerides)
- decreased levels of potassium leading to weakness and an irregular or fast heart beat
- liver problems and toxicity, including liver failure and hepatitis
- hair loss (alopecia).
- increased susceptibility to infection
- easy bruising or bleeding

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or other medical staff.

5. How to store Fluconazole

Your doctor, nurse or pharmacist will usually store your medicine for you.

Keep out of the reach and sight of children.

Do not use FLUCONAZOLE NORIDEM 2 mg/ml after the expiry date which is stated on the carton and the label on the plastic container (bag) after EXP.
The expiry date refers to the last day of that month.

Do not use if the solution is cloudy, discoloured or contains particles.

Store below 25°C. Do not freeze or refrigerate.

Keep the bag in the outer carton to protect from light

For single use only. Use immediately after first opening the bottle.

Chemical and physical in-use stability after dilution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 36 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
Your medicine may be mixed with certain other medicines that may also be given by infusion. Please ask your doctor, nurse or pharmacist if you want any more information about this.

Medicines should not be disposed of via wastewater or Household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Fluconazole contains
The active substance is Fluconazole.
1 ml of solution contains 2 mg of fluconazole

Each 50 ml (millilitre) bag will contain 100 mg (milligram) of Fluconazole. Each 100 ml (millilitre) bag will contain 200 mg (milligram) of Fluconazole.

The other ingredients are Sodium Chloride (see Section 2) and Water for Injections.

What Fluconazole looks like and contents of the pack
Fluconazole 2 mg/ml solution for infusion is a clear and colourless aqueous solution for infusion.

It is a ready to use plastic bag with rubber closures, and aluminium caps.

Pack sizes: 100ml bags (200mg Fluconazole) in packs of 10 bags 200ml bags (400mg Fluconazole) in packs of 10 bags

Not all package sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: To be completed nationally
Manufacturer: To be completed nationally

This medicinal product is authorised in the Member States of the EEA under the following names:
UK: Fluconazole 2mg/ml Solution for infusion
DE: Fluconazol Noridem 2 mg/ml Infusionslösung im Beutel
IE: Fluconazole 2mg/ml Solution for infusion
FR: Fluconazole Noridem 2mg/ml
ES: Fluconazole 2mg/ml Solution for infusion
AT: Fluconazole Noridem 2mg/ml Solution for infusion
GR: Fluconazole Noridem 2mg.ml Solution for infusion

This leaflet was last approved in {MM/YYYY}
<[To be completed nationally]>

UK NATIONAL TEXT:
If this leaflet is difficult to see or read please contact the following address for help:
Fannin, 42-46 Booth Drive  Park Farm South Wellingborough, Northamptonshire NN8 6GT
U.K. Tel +44 118 930 5333

The following information is intended for medical or healthcare professionals only:

For single use only. Discard any unused solution.
The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Fluconazole 2 mg/ml solution for infusion can be infused by means of an infusion system with one of the following solutions and should not be mixed with other medicinal products in a solution infusion.

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Resulting concentration of fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride injection 0.9%</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Dextrose injection 20%</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Lactated Ringer’s injection</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Ringer’s injection</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Potassium chloride 0.3%-Dextrose 5% injection</td>
<td>1.0 mg/ml</td>
</tr>
<tr>
<td>Sodium Bicarbonate 4.2% injection</td>
<td>1.0 mg/ml</td>
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</tbody>
</table>

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 4

Labelling

Module 1.3 – Fluconazole 2mg/ml Solution for Infusion UK/H/1089/01/DC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton and Label:

1. NAME OF THE MEDICINAL PRODUCT

Fluconazole 2mg/ml Solution for Infusion

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2mg fluconazole
Each 100ml [50ml] contains 200mg [100mg] fluconazole

3. LIST OF EXCIPIENTS

Other ingredients: Sodium Chloride (equivalent to 15.4 mmol sodium per 100ml) and Water for Injections.
Please refer to the package leaflet before use

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for Infusion
Each 50 ml bag contains 100 mg of fluconazole
Each 100 ml bag contains 200 mg of fluconazole

Pack sizes of 10 bags

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use
For single use only. Discard any remaining solution.
Read the package leaflet before use.
Use as directed by the physician.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

None

8. EXPIRY DATE
EXP: XXX

Before opening: 2 years
After opening: from a microbiological point of view, the dilutions should be used immediately

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. Do not refrigerate or freeze. Keep the bag in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Noridem Enterprises Ltd., Evagorou & Makariou, Mitsi Building 3, Suit.
115, 1065 Nicosia, Cyprus.

12. MARKETING AUTHORISATION NUMBER(S)

TO BE COMPLETED NATIONALLY

13. BATCH NUMBER

LOT: XXXXXX

14. GENERAL CLASSIFICATION FOR SUPPLY

TO BE COMPLETED NATIONALLY

15. INSTRUCTIONS ON USE

Not applicable

16. INFORMATION IN BRAILLE

Not applicable. For hospital use only.
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Fluconazole 2mg/mL Solution for Infusion in the treatment of mycoses caused by Candida, Cryptococcus and other susceptible yeasts could be approved.

This is an application made under Article 10.1 of Directive 2001/83 EC for Fluconazole 2mg/ml Solution for infusion, claiming to be a generic medicinal product of Diflucan intravenous infusion 2mg/ml, which was granted a licence to Pfizer Ltd in at least one European member state more than 10 years ago. Fluconazole 2mg/ml Solution for infusion is a prescription-only medicine.

With the UK as Reference Member State in this Decentralised Procedure (DCP), the applicant (Noridem Enterprises Limited) gained approval in France, Spain, Greece, Germany, Austria, and Ireland, with the end of procedure (Day210) on 8th October 2009. After a subsequent national phase, the UK granted a licence for this product on 4th November 2009.

Fluconazole belongs to the triazole class of antifungicides, with a mainly fungistatic action. It is a potent and selective inhibitor of ergosterol synthesis in fungi, which leads to defects in the cell membrane. Fluconazole is very specific for fungal cytochrome P450 enzymes.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided justification for non submission of the Risk Management Plan.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Fluconazole Solution for Infusion 2mg/ml |
| Name(s) of the active substance(s) (INN) | fluconazole |
| Pharmacotherapeutic classification (ATC code) | Triazole derivatives J02AC |
| Pharmaceutical form and strength(s) | 2mg/ml Solution for Infusion |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1089/01/DC |
| Reference Member State | United Kingdom |
| Member States concerned | FR, ES, EL, DE, AT and IE |
| Marketing Authorisation Number(s) | PL 24598/0011 |
| Name and address of the authorisation holder | Noredem Enterprises Limited, Evagorou & Makariou, Mitsi Building 3, Suite 115, Nicosia 1065, Cyprus |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

General Information

III.1.1 Nomenclature

INN: Fluconazole

Chemical name: 2-(2,4-difluorophenyl)-1,3-bis-(1H-1,2,4-triazol-1-yl)-2-propanol.

CAS number: 86386-73-4

III.1.2 Structure

![Molecular Structure]

Molecular formula: C_{13}H_{12}F_{2}N_{6}O

Molecular Weight: 306.3

The active substance used in the manufacture of the final product is in compliance with GMP.

A letter of access to the new EDMF is provided.

III.1.3 General properties

White crystalline powder; slightly soluble in water, freely soluble in methanol and soluble in acetone. There are three polymorphs identified (I, II, III), polymorph II is used.
DRUG PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients water for injections and sodium chloride.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients. None of the excipients contain material of animal or human origin.

Pharmaceutical Development
Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the drug product have been compared with those of the originator product. These data demonstrate that the proposed product can be considered a generic medicinal product of Diflucan Intravenous Infusion 2mg/ml (Pfizer LTD).

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packed in plastic bags of polypropylene with rubber (type I) closures, and aluminium caps with caps with plastic flip-top covers. Pack sizes of 10 bags

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with guidelines concerning materials in contact with parenteral products.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set for the unopened product, with the storage instructions ‘Protect from light’, ‘Store below 25 degrees C’ and ‘Keep container in the outer carton’.

Conclusion
It is recommended that Marketing Authorisation is granted for this application.

The requirements for a generic product of the proposed and originator product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar physico-chemical properties have been demonstrated for the proposed and originator product.
III.2 PRE-CLINICAL ASPECTS
This application claims to be a generic medicinal product of Diflucan Intravenous Infusion 2mg/ml (Pfizer LTD), which has been licensed within the EU for over 10 years.

No new preclinical data have been supplied with this application, however, a preclinical expert report summarising relevant non-clinical studies has been included in the dossier; this is satisfactory.

III.3 CLINICAL ASPECTS
III.3.1 Clinical Pharmacology
No new data have been submitted and none are required.

No bioequivalence study has been submitted. As this is solution for infusion, no bioequivalence study is required.

III.3.2 Clinical Efficacy
No new data have been submitted and none are required.

III.3.3 Clinical Safety
No new data have been submitted and none are required.

Module 1 – Administrative information

MAA forms
The MAA form is medically satisfactory.

Summary of Product Characteristics (SPC)
The SPC is medically satisfactory and consistent with that for the reference product.

Patient Information Leaflet (PIL)
The PIL is medically satisfactory and consistent with the SPC.

Packaging
The packaging is medically satisfactory.

Module 2 – Clinical overall summary
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of Module 5.

Conclusions on safety
The medical assessor recommended that marketing authorisation was granted for this product.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Fluconazole 2mg/ml Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical studies were conducted. The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Fluconazole 2mg/ml Solution for Infusion beyond the already well-described effects of fluconazole.

EFFICACY
No new or unexpected safety concerns arise from this application.

The SPC and PIL are satisfactory and consistent with those of the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with fluconazole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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