SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

NEOZOLE® (Fluconazole BP 200mg/100ml Injection)

Strength

Each 100 ml contains:

Fluconazole BP ……200mg

Sodium Chloride BP……900mg

Pharmaceutical/Dosage form

Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 ml contains:

Fluconazole BP ……200mg

Sodium Chloride BP……900mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection.

A clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neozole Injection is indicated for treatment 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 anti-fungal 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 anti-fungal 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/Dosage and method of administration

Posology

Treatment with **Neozole Injection** 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 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 Administer For An Adult Treated By The Intravenous Route

Treatment with **Neozole Injection** 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**
Invasive candidiasis				
- Candidaemia, disseminated candidiasis and other forms of invasive candida infection	800	400	Dependent upon clinical response	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms of candidema.
Severe mucosal candidiasis				**Use only when oral dosing is not possible.**
- Oropharyngeal candidiasis	200-400	100-200	7-21 days	Use until oropharyngeal candidiasis is in remission. Longer periods may be used in patients with severely compromised immune function.
- Oesophageal candidiasis	200-400	100-200	14-30 days	Use until oesophageal candidiasis is in remission. Longer periods may be used in patients with severely compromised immune function. Longer periods may be used in patients with severely compromised immune function. Longer periods depending on both the severity of infection or underlying immune compromisation and infection.
- Candiduria	200-400	200-400	7-21 days	
- Chronic atrophic candidiasis	50	50	14 days	
- Chronic mucocutaneous candidiasis	50-100	50-100	up to 28 days	
Prevention of relapses in patients infected with HIV who are at high risk of relapses - Oropharyngeal candidiasis	100-200	100-200 daily or 200 3 times per week	Indefinitely	Treatment may be for an indefinite period for patients with chronic immune suppression
- Oesophageal candidiasis	100-200	100-200 daily or 200 3 times per week	Indefinitely	Treatment may be for an indefinite period for patients with chronic immune suppression
Treatment of cryptococcal meningitis				
• Initial therapy	400	200-400	Typical 6-8 weeks	Duration of treatment will depend upon clinical and mycological response. In life threatening infections the daily dose can be increased to 800mg.
• Maintenance therapy to prevent relapses in patients with high risk of recurrence		200	Indefinitely	
Prophylaxis against deep candida infections				
• In patients with neutropenia due to bone marrow transplantation	400	200-400	See additional guidance	Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for seven days after the neutrophil count rises above 1000 cells per mm^3.
• *Coccidioidomycosis*	200-400	200-400	11-24 months or longer depending on the patient	800mg daily may be considered for some infections and especially meningeal disease.

Paediatric population

A maximum daily dose of 400mg should not be exceeded in paediatric population.

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.

For paediatric patients with impaired renal function, see dosing in “Patients *with impaired renal function*” . The pharmacokinetics of fluconazole have not been studied in paediatric population with renal insufficiency.

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 (0-27 days)	Note: Neonates excrete fluconazole slowly.		
• 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 to 11 years			
	• Mucosal candidiasis	3 mg/kg/day.	On the first day a loading dose of 6 mg/kg may be given in order to more rapidly reach a steady state.
	• Invasive candidiasis • Cryptococcal meningitis	6-12 mg/kg/day	Depending on the severity of the disease
	• Maintenance therapy to prevent relapses of Cryptococcal meningitis in children with high risk of recurrence	6mg/kg/day	Depending on the severity of the disease
	• Prophylaxis of Candida in immunocompromised patients	3-12 mg/kg/day	Depending on the extent and duration of the induced neutropenia (see adults posology)

Adolescents (from 12 to 17 years old):

Depending on weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200, and 400mg in adults corresponds to a 3, 6 and 12mg/kg dose in children to obtain a comparable systemic exposure.

Renal impairment

Fluconazole is cleared primarily by renal excretion as an 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) is based on the table below:

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%
≤ 50(no dialysis)	50%
Patients receiving dialysis	100% after every dialysis session

Patients on regular dialysis should receive 100% of the recommended dose after each dialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance.

Hepatic impairment:

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.

Method of 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 restrictions, 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 the active substance, other azole compounds or to any of the excipients listed in section 6.1

Co-administration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see Sections 4.4 and 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.

Tinea capitis

Fluconazole has been studied for the treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Fluconazole should not be used for *tinea capitis*.

Cryptococcosis

The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.

Candidiasis

Studies have shown an increasing prevalence of infections with *Candida* species other than *C. albicans.* These are often inherently resistant (e.g. *C. krusei and C. auris*) or show reduced susceptibility to fluconazole (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to consider the prevalence of resistance in various *Candida* species to fluconazole.

Deep endemic mycoses

The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as Para coccidioidomycosis, lymphocutaneous, sporotrichosis and histoplasmosis is limited, which prevents specific dosing recommendations.

Hepatobiliary system

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. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

The patient should be informed of suggestive symptoms of serious hepatic effects (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued, and the patient should consult a physician.

Cardiovascular system

Certain azoles, including fluconazole, have been associated with prolongation of the QT-interval. During post marketing surveillance, there have been rare cases of torsade de pointes 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 and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

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

Dermatological reactions

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.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported.

Halofantrine

Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended (see section 4.5).

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also, although rarely seen be applicable to fluconazole.

Adrenal insufficiency relating to concomitant treatment with Prednisone is described in section 4.5. The effect of fluconazole on other medicinal products.

Cytochrome P450

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, CYP2C19 and/or CYP3A4 should be closely monitored (see sections 4.3 and 4.5).

Hypersensitivity

Rare instances of anaphylactic reactions have been reported (see section 4.8).

Pregnancy

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

Paediatric population

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.

Cryptococcal meningitis

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.

Terfenadine

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

Excipients

This medicinal product contains 15.4 mmol (354 mg) sodium per 100 ml of solution. To be considered 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. Fluconazole is also an inhibitor of the isozyme CYP2C19 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.

Concomitant use of the following other medicinal products is contraindicated

Astemizole (CYP3A4-substrate):

Astemizole overdoses have led to prolonged QT intervals such 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.

Pimozide and Quinidine:

Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of Torsades de Pointes. Co-administration of fluconazole and pimozide is contraindicated (see section 4.3).

Erythromycin:

Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. Co-administration of fluconazole and erythromycin is contraindicated (see section 4.3).

Halofantrine:

Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. This combination should be avoided (see section 4.4).

Concomitant use of the following other medicinal products lead to precautions and dose adjustments

The effects of other medicinal products on fluconazole:

Hydrochlorothiazide:

In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretic.

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.

Concomitant use of the following other medicinal products cannot be recommended

Amiodarone: concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be taken when both drugs are combined, notably with high dose fluconazole (800 mg).

The effects of fluconazole on other medicinal products:

Alfentanil (CYP3A4-substrate):

In concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µ g/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.

Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed a small additive antifungal effect in systemic infection with C.albicans, no interaction in intracranial infection with Cryptococcus neoformans.

Amitriptyline (CYP2D6-substrate):

Several case histories 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

In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9.

In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

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. Frequent monitoring for adverse events is recommended.

Carbamazepine (CYP3A4-substrate):

Carbamazepine is metabolized by isozyme CYP3A4. Fluconazole is thus likely to cause carbamazepine toxicity, probably due to inhibition of isozyme CYP3A4. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effects.

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.

Cyclophospamide:

Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl:

One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

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.

Everolimus:

Although not studied in vivo or in vitro, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

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.

HMG-CoA-reductase-inhibitors (CYP2C9- or CYP3A4-substrate):

The risk of myopathy and rhabdomyolysis 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 because 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 regarding 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 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 the reinforced impact of methadone after concomitant administration of fluconazole and methadone. A pharmacokinetics study showed an increased AUC of methadone (35% on average). Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs:

The Cmax and AUC of flurbiprofen increased by 23% and 81%, respectively, when co-administered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] increased by 15% and 82%, respectively, when fluconazole was co-administered with racemic ibuprofen (400mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

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.

Saquinavir:

Fluconazole increases the AUC and Cmax of saquinavir with approximately 50% and 55% respectively, due to the inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

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.

Vinca Alkaloids:

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

Vitamin A:

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

Voriconazole (CYP2C9 and CYP3A4 inhibitor):

Co administration of oral voriconazole (400mg Q12h for 1 day, then 200mg Q12h for 2.5 days) and oral fluconazole (400mg on day 1, then 200mg Q24 for 4 days) to 8 healthy male subjects resulted in an increase in Cmax and AUC of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

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 fluconazole 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 receive 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.

Azithromycin:

An open label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

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 Fertility, pregnancy and lactation

Women of childbearing potential

Before initiating treatment, the patient should be informed of the potential risk to the fetus.

After single dose treatment, a washout period of 1 week (corresponding to 5-6 half-lives) is recommended before becoming pregnant (see section 5.2).

For longer courses of treatment, contraception may be considered, as appropriate, in women of childbearing potential throughout the treatment period and for 1 week after the final dose.

Pregnancy

Observational studies suggest an increased risk of spontaneous abortion in women treated with fluconazole during the first and/or second trimester compared to women not treated with fluconazole or treated with topical azoles during the same period.

Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤ 450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.

Available epidemiological studies on cardiac malformations with use of fluconazole during pregnancy provide inconsistent results. However, a meta-analysis of 5 observational studies including several thousand pregnant women exposed to fluconazole during the first trimester finds a 1.8-2-fold increased risk of cardiac malformations when compared to no fluconazole use and/or topical azoles use.

Case reports describe a pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during pregnancy for 3 months or more, in the treatment of coccidioidomycosis. The birth defects seen in these infants include brachycephaly, ears dysplasia, giant anterior fontanelles, femoral bowing and radio-humeral synostosis. A causal relationship between fluconazole use and these birth defects is uncertain.

Fluconazole in standard doses and short-term treatment should not be used during pregnancy unless clearly necessary.

Fluconazole in high doses and/or in prolonged regimens should not be used during pregnancy except for life threatening infections.

Breast-feeding

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 high-dose fluconazole.

Fertility

Fluconazole did not affect the fertility of male or female rats (see section 5.3).

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.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section 4.4).

System Organ Classes	Very common ≥ 1/10	Common ≥ 1/100, <1/10	Uncommon ≥ 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, leukopenia, neutropenia, thrombocytopenia		
Immune system disorders				Anaphylactic reactions, itching	Angioedema, face oedema	Urticaria
Metabolism and nutritional disorders			Decreased appetite	Hypercholesterolemia, hypertriglyceridemia, hypokalaemia		
Psychiatric disorders			Insomnia, somnolence			
Nervous system disorders		Headache	Convulsions, seizures, dizziness, paraesthesia, taste perversion,	Tremor		
Ear and labyrinth disorders			Vertigo			
Cardiac disorders				Ventricular arrthythmia (QT prolongation, Torsade de Pointes)		
Gastrointestinal disorders		Nausea, vomiting, abdominal pain and diarrhoea	Dyspepsia, flatulence, anorexia, constipation, dry mouth			
Hepatobiliary disorders		Elevated alkaline phosphatase, ASAT and ALAT	Cholestasis, hepatocellular damage, jaundice, clinically significant increase of total bilirubin	Hepatic toxicity, hepatic nacrosis, hepatic failure, hepatitis, hepatocellular necrosis, hepatocellular damage.		
Skin and subcutaneous tissue disorders		(maculopapular erythema) rash	Drug eruption*, urticaria, pruritis, increased sweating	Angioedema, toxic epidermal necrolysis, Stevens - Johnson syndrome, acute generalized exanthematous pustulosis dermatitis exfoliative, face oedema, alopecia		Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Myalgia			
Renal and urinary disorders			Changes in renal function tests			
General disorders and administration site conditions			Fatigue, malaise, asthenia, fever			

* Including Fixed Drug Eruption

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.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisations of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Symptoms

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 were resolved within 48 hours.

Management

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

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives,

ATC code: J02A CO1.

Mechanism of action

Fluconazole is a member of the triazole class of antifungal agents with primarily fungistatic effects. It is a potent and selective inhibitor of the synthesis of fungal ergosterol which leads to defects in the cell membrane. Fluconazole is highly specific for fungal cytochrome P-450 enzymes.

Fluconazole 50mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200mg to 400mg daily has no clinically significant effect on endogenous steroid levels on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50mg do not affect its metabolism.

Resistance mechanism

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. There have been reports of superinfection with *Candida* species other than *C. albicans*, which often have inherently reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g. *C. krusei, C. auris*). Such infections may require alternative antifungal therapy. 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 principal 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.

Antifungal susceptibility

[Source: Pfaller et al, 2006: ARTEMIS DISK Global Antifungal Surveillance Study.

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 several 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

C. glabrata shows reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole.

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.

Paediatric population

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.

Elderly:

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50mg oral dose of fluconazole. Ten of these patients were receiving diuretics. The Cmax was 1.54µ g/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4± 20.3µ g• h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetics parameter values are higher than analogous values reported for normal young male volunteers. Co-administration of diuretics did not significantly alter AUC or Cmax. In addition, creatinine clearance (74ml/min), the percent of medicinal product recovered unchanged in urine (0-24hr, 22%) and the fluconazole renal clearance estimates (0.124ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reducing renal function characteristics of this group.

Renal impairment:

In patients with severe renal insufficiency, (GFR<20ml/min) half-life increased from 30 to 98 hours. Consequently, a reduction of dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

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.

Carcinogenesis:

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10mg/kg/day had an increased incidence of hepatocellular adenomas.

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

S.NO	Composition	Reference
1.	Sodium Chloride	BP
2.	Water for Injection	BP

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:

3 years

6.4 Special precautions for storage

Store below 30°C and protect from light, do not refrigerate or freeze

6.5 Nature and contents of container

LDPE (Low-density polyethylene) bottle.

Pack sizes: 100ml.

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 solutions 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 a 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. APPLICANT/HOLDER OF CERTIFICATE PRODUCT REGISTRATION.

Unique Pharmaceuticals Limited
11, Fatai Atere Way, Matori-Mushin Lagos
Tel: +234 8097421000
Email: mail@uniquepharm.com

8. DRUG PRODUCT MANUFACTURER

Unique Pharmaceuticals Limited
Km 38, Abeokuta Road, Sango-Ota,
Ogun State, Nigeria.
Tel: +234 8097421000
Email: mail@uniquepharm.com

9. NAFDAC REGISTRATION NUMBER(S)

04-3501

10. DATE OF REVISION OF THE TEXT

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