1. Name of the Medicinal Product

NKOYO FLUCONAZOLE

(Fluconazole USP 150 mg Tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch Size: 407.000 Kg (5, 50,000 Tablets)

S.N.	Name of Raw Material	Reference	Unit Formula (mg)	Batch Formula (Kg)
Active Material				
1	Fluconazole	USP	150.000	187.500
In-Active Material				
2	Dibasic Calcium Phosphate	IH	190.00	104.500
3	Maize Starch	BP	274.560	151.008
4	Microcrystalline Cellulose	BP	96.000	52.800
5	Propyl Paraben	BP	0.400	0.220
6	Methyl Paraben	IH	0.040	0.022
7	Purified Water	IH	q.s.	98.00
8	Purified Talc	BP	10.000	5.500
9	Sodium Starch Glycolate	BP	10.000	5.500
10	Magnesium Stearate	BP	9.000	4.950
	Weight of Compressed Tablet		**740.000**	**407.000**

3. PHARMACEUTICAL FORM

Oral dosage form (Uncoated Tablet)

Description: White Caplet Shape, Compressed tablets, debossed "Break line' on one side & 'MAXHEAL' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nkoyo Fluconazole is indicated for the treatment of systemic candidiasis, mucosal candidiasis & cryptococcosis, vaginal candidiasis, fungal infections in patients with malignancy.

4.2 Posology and method of administration

Oropharyngeal or Oesophageal candidiasis: 200 mg on the first day followed by 100 mg once daily. Maximum of 400mg/day.

Vaginal candidiasis: 150 mg once oral dose.

Deep seated candidiasis: 400mg on the first day followed by 200mg once daily for 4 weeks.

Continue for another 2 weeks after resolution of symptoms.

Cryptococcal meningitis: 400mg on the first day followed by 200mg once daily. Maximum of 400mg/day for 10-12 weeks.

Neutropenic cancer: 50 - 100mg once daily.

4.3 Contraindications

Nkoyo Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing Nkoyo Fluconazole to patients with hypersensitivity to other azoles. Co-administration with terfenadine is contraindicated in patients receiving Nkoyo Fluconazole at multiple doses of 400 mg or higher based on results of a multiple dose interaction study. Co-administration with cisapride is also contraindicated in patients receiving Nkoyo Fluconazole.

4.4 Special warnings and precautions for use

Renal system

Fluconazole should be administered with caution to patients with renal dysfunction (see section 4.2).

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'.**

Hepatobiliary system

Fluconazole should be administered with caution to patients with liver dysfunction. Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy should be monitored closely for the development of more serious hepatic injury. The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Fluconazole should be discontinued immediately if clinical signs or symptoms consistent with liver disease develop that may be attributable to fluconazole and the patient should consult a physician.

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. During post- marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medicines that may have been contributory. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and *torsades de pointes*.

Fluconazole should be administered with caution to patients with these potentially proarrythmic conditions.

Coadministration of other medicinal products 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).

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).

Dermatological reactions

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

Hypersensitivity

In rare cases, as with other azoles, anaphylaxis has been reported (see section 4.3).

Cytochrome P450

Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with drugs with a narrow

therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5 Interaction with Other Medicaments and Other Forms of Interaction)

Terfenadine

The coadministration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored (see section 4.3 Contraindications and 4.5 Interaction with Other Medicaments and Other Forms of Interaction).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200mg once daily and cisapride 20mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QT interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

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

Quinidine: Although not studied in vitro or in vivo, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with

QT prolongation and rare occurrences of torsades de pointes. Coadministration of fluconazole and quinidine 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. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).

Concomitant use of the following other medicinal products cannot be recommended:

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 that should be used with caution:

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 (800mg).

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

The effect 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 concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.

Rifampicin: Concomitant administration of fluconazole and rifampicin resulting in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.

Interaction studies have shown that when oral fluconazole is coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

The effect of fluconazole on other medicinal products

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19.In addition to the observed/documented interactions mentioned below there is a risk of increased plasma concentration of other compounds metabolised by CYP2C9, CYP2C19 and CYP3A4 co- administered

with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (See section 4.3)

Alfentanil: A study observed a reduction in clearance and distribution volume as well as prolongation of T½ of alfentanil following concomitant treatment with fluconazole. During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 μg/kg) in healthy volunteers the alfentanil AUC 10 increased 2-fold. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with C. albicans, no interaction in intracranial infection with Cryptococcus neoformans, and antagonism of the two drugs in systemic infection with A.fumigatus. The clinical significance of results obtained in these studies is unknown.

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 (Short Acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in

Patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentrating measurements/effect.

Calcium Channel Blockers: Certain dihydropyridine calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolised by CYP3A4. Fluconazole has the potential to increase thesystemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Celecoxib: During concomitant treatment with fluconazole (200mg daily) and celecoxib (200mg) the celecoxib Cmax and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

Cyclophosphamide: 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 possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomised crossover study with twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly.

Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dosage of ciclosporin depending on ciclosporin concentration.

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

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously.

Increased tacrolimus levels have been associated with nephrotoxicity. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone: Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The Cmax and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer (S-(+)-ibuprofen) was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure or other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac).

Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC24 by 75% and Cmin by 128%.With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplant patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and Cmax of saquinavir with approximately 50% and 55% respectively, due to 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. Dosage adjustment of saquinavir may be necessary.

Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g. chlorpropamide, glibenclamide, glipizide, and tolbutamide) in healthy volunteers.

Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during co-administration.

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 rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

Tofacitinib: Exposure of tofacitinib is increased when tofacitinib is co-administered with medications that result in both moderate inhibition of CYP3A4 and strong inhibition of CYP2C19 (e.g.

fluconazole). Therefore, it is recommended to reduce tofacitinib dose to 5 mg once daily when it is combined with these drugs.

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-retinoic acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole*:* (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUCτ 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.

Zidovudine: Fluconazole increases Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.

Azithromycin: An open-label, randomised, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200mg oral dose of azithromycin on the pharmacokinetics of a single 800mg 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.

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

Ivacaftor: Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

4.6 Pregnancy and lactation

Pregnancy

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3)

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

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

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast- feeding may be maintained after a single use of a standard dose 150 mg fluconazole or less. Breast- feeding is not recommended after repeated use or after high dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Fluconazole and any potential adverse effects on the breast-fed child from Fluconazole or from the underlying maternal condition.

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

No studies have been performed on the effects of Fluconazole on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Fluconazole and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities (see section 4.4 Special Warnings and Special Precautions for Use) have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

The following undesirable effects have been observed and reported during treatment with fluconazole with the following frequencies: Very common (≥1/10); common (≥1/100 to ≤1/10); uncommon (≥1/1000, <1/100) rare (≥1/10000, <1/1000) and very rare (<1/10000) not known (cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	Uncommon	Anaemia
	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
	Rare	Hypertriglyceridaemia, Hypercholeosterolaemia Hypokalaemia
Psychiatric disorders	Uncommon	Insomnia, somnolence
Nervous system disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, taste perversion
	Rare	Tremor
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Rare	Torsade de pointes, QT prolongation
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, vomiting
	Uncommon	Dyspepsia, flatulence, dry mouth, constipation
Hepato-biliary disorders	Common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
	Uncommon	Cholestasis, jaundice, bilirubin increased
	Rare	Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage
Skin and subcutaneous tissue disorders	Common	Rash

	Uncommon	Pruritus, urticaria, increased sweating, drug eruption*
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, connective tissue and bone disorders	Uncommon	Myalgia
General disorders and administration site conditions	Uncommon	Fatigue, malaise, asthenia, fever

** Including Fixed Drug Eruption*

Paediatric Population

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

4.9 Overdose

There have been reports of overdose with fluconazole and hallucination and paranoid behaviour have been concomitantly reported.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

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

5. Pharmacological properties

5.1 Pharmacodynamics properties

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

Mechanism of action

Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450- mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Fluconazole 50 mg 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 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH

stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Susceptibility in *vitro*:

In vitro, fluconazole displays antifungal activity against most clinically common Candida species (including C. albicans, C. parapsilosis, and C. tropicalis). C. glabrata shows a wide range of susceptibility while C. krusei is resistant to fluconazole.

Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus. Gattii as well as the endemic moulds Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum and Paracoccidioides brasiliensis.

Pharmacokinetic/pharmacodynamic relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to Candida spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

5.2 Pharmacokinetic properties

Absorption

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

Absorption

After oral administration fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral administration is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 – 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4 – 5 with multiple once daily dosing.

The administration of a loading dose on the first day, double that of the normal daily dose, raises plasma levels to approximate to 90% steady-state levels by the second day.

Distribution

The apparent volume of distribution approximates 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, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 μg /g and 7 days after cessation of treatment the concentration was still 5.8 μg /g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 μg/g and 7 days after the second dose was still 7.1 μg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 μg/g in healthy and 1.8 μg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Elimination

Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

Its long plasma elimination half-life makes it possible to administer a single dose in the treatment of vaginal candidiasis, once daily and once weekly dosing for other indications.

A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a tablet or in an oral suspension by rinsing and retaining in the mouth for 2 minutes and swallowing.

The maximum concentration of fluconazole in saliva after the suspension was observed five minutes after ingestion and was 182 times higher than maximum saliva concentrations after the tablet, which occurred four hours after ingestion.

After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the tablet. There was no significant

difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR< 20 ml/min) half-life increased from 30 to 98 hours. Consequently, reduction of the 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.

Pharmacokinetics during lactation

A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of Diflucan. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multipledose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study. After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 μg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg. Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44- 185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml)

was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased 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.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The Cmax was 1.54 μg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 μg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministation of diuretics did not significantly alter AUC or Cmax. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/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 reduce renal function characteristics of this group.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

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.

Mutagenesis*:* Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S .typhimurium* and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 ug/ml) showed no evidence of chromosomal mutations.

Reproductive toxicity: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg.

Increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to

320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still- born pups and decrease of neonatal survival at these doses. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

6. Pharmaceutical Particulars

6.1. List of excipients

Dibasic Calcium Phosphate
Maize Starch
Microcrystalline Cellulose
Propyl Paraben
Methyl Paraben
Purified Talc
Sodium Starch Glycolate
Magnesium Stearate

6.2. Incompatibilities

None

6.3. Shelf life

36 Months.

6.4 Special precautions for storage

Store below above 30^{o}C. Protect from light.

6.5. Nature and contents of container

Aluminium - Aluminium Blister Pack
10 Tablets are packed with Aluminium- Aluminium blister along with pack insert.
Pack Size: 1X10

6.6. Special Precaution for Disposal

No special requirement

7. APPLICANT/MANUFACTURER

NAFDAC REG.NO: A4-0421
MANUFACTURED BY:
MAXHEAL LABORATORIES PVT LTD
Plot No. - 2-7/80-85, Sursez, G.I.D.C
Sachin, Surat Gujarat-394230.India