

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NAZOFLUC-150 (Fluconazole Capsules 150 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Hard Gelatin Capsule Contains:

Fluconazole USP 150 mg

Excipient with known effect: Each hard gelatin capsule contains 100 mg Lactose BP

For the list of excipients, see section 6.1.

Batch size: 100,000 capsules

Actual quantities per batch: Fluconazole USP 15.00 kg, Lactose BP 10.00 kg, total filled powder 25.000 kg, and empty hard gelatin capsule shells 100,000 Nos.

Actual quantities per capsule: Fluconazole USP 150 mg, Lactose BP 100 mg, total filled powder 250 mg, and empty hard gelatin capsule shell 1 Nos.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

Pink/White coloured size “2” hard gelatin capsule containing white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

NAZOFLUC 150 is indicated for the treatment of the following conditions:

Vaginal candidiasis, acute or recurrent; or candidal balanitis associated with vaginal candidiasis.

4.2 Posology and method of administration

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4.3 Contraindications

Fluconazole should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or to any of the other ingredients.

Co-administration of terfenadine is contra-indicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Co-administration of other drugs known to prolong the QT interval and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, pimozide and quinidine are contraindicated in patients receiving fluconazole (see Special Warnings and Special Precautions for Use and Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

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 for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to fluconazole.

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 develops in a patient treated for a superficial fungal infection which is considered attributable to fluconazole, 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.

The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

In rare cases, as with other azoles, anaphylaxis has been reported.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. 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 medications that may have been contributory. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions

Use with caution in patients with renal impairment.

The capsules contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, LAPP lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose fluconazole 150mg has not yet been established:

Concomitant use of the following other medicinal product is contraindicated:

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

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 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3 Contraindications). The coadministration of fluconazole at doses lower than 400 mg 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.

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.

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. This combination should be avoided.

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 kinetic 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, although the prescriber should bear it in mind.

Rifampicin

Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients

receiving concomitant rifampicin, an increase in the fluconazole dose should be considered.

The effect of fluconazole on other medicinal products

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 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 $T_{1/2}$ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 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 an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. As with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melaena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored. Dose adjustment of warfarin may be necessary.

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.

Benzodiazepines (Short acting)

Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects.

This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patients should be appropriately monitored. Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, C_{max} with 20-32% and increases t_{1/2} by 25-50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

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 concentration measurements/effect.

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

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

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. This combination may be used by reducing the dosage of ciclosporin depending on ciclosporin concentration.

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.

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

Fentanyl: One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomized crossover study with twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

Concomitant use of the following other medicinal product 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.

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.

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

Oral contraceptives

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

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted 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 coadministered.

In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC of saquinavir with approximately 50%, C_{max} with approximately 55% and decreases clearance of saquinavir with approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

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.

Sulphonylureas

Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during coadministration.

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.

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 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 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 AUC_t 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 C_{max} and AUC of zidovudine by 85% and 75%, 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.

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

4.6 Fertility, pregnancy and lactation

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4.7 Effects on ability to drive and use machines

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4.8 Undesirable effects

Fluconazole is generally well tolerated.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

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

System Order Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
	Uncommon	Anaemia
Immune system disorders	Rare	Anaphylaxis
Metabolism & nutrition disorders	Uncommon	Decreased Appetite

	Rare	Hypertriglyceridaemia, Hypercholesterolaemia Hypokalemia
Psychiatric disorders	Uncommon	Insomnia, somnolence
Nervous system disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, taste perversion
	Rare	Tremor
Ear & 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
Hepatobiliary 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 & subcutaneous tissue disorders	Common	Rash
	Uncommon	Pruritus, urticaria, increased sweating, drug eruption
	Rare	Toxic epidermal necrolysis , Stevens-Johnson syndrome, acute generalized exanthematous- pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal, connective tissue & bone disorders	Uncommon	Myalgia
General & administration site disorders	Uncommon	Fatigue, malaise, asthenia, fever

Paediatric Population

The pattern and incidence of side effects and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication are comparable to those seen in adults.

Health care professionals are asked to report any suspected adverse reactions via the <https://pv.pharmacyboardkenya.org>

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic Group

Anti-Fungal agents, Antimycotics for systemic use

ATC code

D01AC15

5.1 Pharmacodynamic propertiesMechanism 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.

In vitro, fluconazole displays antifungal activity against most clinically common *Candida* species (including *C. albicans*, *C. parapsilosis*, *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 dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

PK/PD 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.

Mechanism(s) of resistance

Candida has developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

There have been reports of super infection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to fluconazole (e.g. *Candida krusei*). Such cases may require alternative antifungal therapy.

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 absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.

Distribution:

The apparent volume of distribution approximates to total body water. The 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% the corresponding plasma levels.

High skin concentration of fluconazole, above serum concentrations, is achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg 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.

Excretion

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 medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.

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 in Children

Pharmacokinetic data were assessed for 113 pediatric patients from 5 studies; 2 single dose studies, 2 multiple dose studies and a study in premature neonates. Data from 1 study were not interpretable due to changes in formulation partway through the study. Additional data were available from a compassionate use study.

After administration of 2 - 8 mg/kg fluconazole to children between 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/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Name of Material	Specification
Lactose	BP
Hard gelatin capsule shell	IHS

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C. Keep all medicines out of reach of children.

6.5 Nature and contents of container

NAZOFLUC 150 is packed in 1 X 1 Alu - PVC Blister in printed carton along with package insert.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

SALAMA PHARMACEUTICALS LTD

8. MARKETING AUTHORISATION NUMBER(S)

H2022/CTD6659/12991

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

2023 February 20

10. DATE OF REVISION OF THE TEXT

2023 February 20