Summary of product characteristics

1 Name of the medicinal product
Fluconazole capsules BP 150mg

2 Qualitative and quantitative composition
Eachhard gelatin capsules contains Fluconazole 150mg

Excipients with known effects; Each hard capsule also contains Lactose monohydrate

For complete list of excipients, see section 6.1

3 Pharmaceutical form
Hard gelatin capsule

Light blue (cap)/ white (body) colored, hard gelatin capsules filled with white to colored free flowing granules.

4 Clinical Parameters
4.1Therapeutic indications
Fluconazole capsules is an azole antifungal medication indicated for the treatment of serious fungal or yeast infections present in the vagina, mouth or throat, lungs, bladder or blood. Such conditions include vaginal candidiasis, oropharyngeal candidiasis, esophageal candidiasis, cryptococcal meningitis. Fluconazole could also be used to prevent fungal infections in immunocompromised patients.

4.2 Posology/ method of administration
Adult dosage

Vaginal infections

Vaginal infections can be treated with a stat dose of 150mg as a single oral dose and 150mg monthly to prevent recurrence.

Oropharyngeal candidiasis

Fluconazole 150mg should be administered on the first day followed by a 100mg dose once daily. This condition generally resolves after several days but should not be discontinued until after at least two weeks to decrease the risk of relapse.

Esophageal candidiasis

Fluconazole 150mg should be administered on the first day followed by 100mg once daily. Dosages of up to 12mg/kg/day may be used. Treatment should be continued for a minimum of 3 weeks and at least two weeks after symptoms have been resolved.

Urinary tract infections and peritonitis

Fluconazole 50mg to 150mg a day should be administered.

Cryptococcal meningitis

Fluconazole 400mg on the first day followed 150mg once daily should be given.

Tinea pedis, tinea corporis, Tinea cruis and other Candida infections

50mg once daily or 150mg once weekly for 6 weeks should be administered

Tinea versicolor

300mg-400mg once daily 3 weeks should be administered.

Special populations

Elderly

Renal function should determine the dosage in elderly population

Renal impairment

Fluconazole is excreted unchanged as an active substance in urine. Single dose therapy does not require dosage adjustment. For multi-dose therapy, a loading dose of 50mg to 400mg should be administered, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following parameters;

- For creatinine clearance >50ml/min, 100% of the recommended dose should be administered
- For creatinine clearance <50ml/min 50% of the recommended dose should be administered.
- For Hemodialysis patients, 100% of the recommended dose cand be given after hemodialysis. On days when hemodialysis is not done patients should receive a reduced dose.

Hepatic impairment

There is limited data on for patients with liver impairment, as such Fluconazole should be administered with caution to patients with liver dysfunction. See section 4.4 for more information.

Paediatricpopulation

The maximum daily dosage for the paediatric population is 400mg.

The duration of treatment is determined by the clinical and mycological response, just as similar infections in adults.

For cases of impaired renal functions in paediatric patients, see dosing in "*Renal impairment"*

Children (28 days to 11years)

Mucosal candidiasis including oropharyngeal and esophageal candidiasis

An initial dose of 6mg/kg should be given followed by a dose of 3mg/kg once daily.

Cryptococcal meningitis

A dose of 6 to 12mg/kg once daily should be given.

Prophylaxis of candida in immunocompromised patients

A dose of 3 to 12mg/kg once daily should be used

Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence

A dose of 6mg/kg should be administered once daily.

Term Newborn infants (0 to 27 days)

The rate of excretion for neonates is slow. There is limited clinical data to support this dosage. See section below.

- Newborn infants (0 to 14 days): The same dose as given to pediatric population (6 months to 11 years) should be administered every 72 hours. A maximum daily dose of 12mg/kg every 72 hours should be maintained.
- Newborn infants (15 to 27days): The same dose as given to pediatric population (6months to 11 years) should be administered every 48 hours. A maximum daily dose of 12mg/kg every 48 hours should be maintained.

Adolescents from 12 to 17years old

The posology of adolescents is determined by the clinician based on the weight and pubertal development of the age group. Clinical evidence shows that children have higher clearance for fluconazole than adults. Doses of 100,150 and 400mg in adults corresponds to a 3,6 and 12mg/kg dose in adolescents for a similar systemic exposure.

There is no clinical evidence for the safety and efficacy of Fluconazole in the pediatric population. For genital candidiasis in adolescent, if treatment for genital candidiasis is imperative adult dosage can be used.

4.3 Contraindications

Fluconazole is contraindicated in patients with known hypersensitivity to fluconazole and its inactive ingredients

Fluconazole should be prescribed with caution to patients with hypersensitivity toother azoles. Based on the findings of a multiple dose interaction study, coadministration of terfenadine is not recommended for patients receiving Fluconazole pill at multiple doses of 400 mg per day or higher.For medicinal products known to prolong the QT interval and which are metabolised by the Cytochrochrome P450 co-enzyme (CYP) 3A4 such as Cisapride, Astemizole, Pimozole, Quinidine and Erythromycin co-administration of fluconazole is contraindicated. See **section 4.5** (interaction with other medicinal product) for more information.

4.4 Special warnings and precautions of use

Fluconazole should not be used during pregnancy unless the patient has a serious or possibly fatal fungal infection, in which case it may be administered if the expected benefit justifies any potential risks to the unborn child.

Women of child-bearing age should think about using effective contraceptive methods and should continue for the duration of the treatment and for roughly one week (five to six half-lives) after the last dosage. Refer below on lactation, pregnancy, and fertility.

Patients with liver disease should take fluconazole with caution. Fluconazole has seldom been linked to fatal cases of severe liver toxicity, mostly in individuals with significant underlying health issues. There has been no discernible correlation found between the total daily dose, duration of therapy, patient age, or sex in cases of fluconazole-associated hepatotoxicity. Typically, fluconazole hepatotoxicity has been reversible when stopping therapy. When taking fluconazole, patients who experience abnormal liver function tests should be monitored for the emergence of more severe liver damage.

If clinical indications or symptoms of liver disease appear that could be related to fluconazole, then fluconazole should be discontinued.

Patients have rarely experienced cutaneous exfoliation reactions, like Stevens-Johnson syndrome and toxic epidermal necrolysis while receiving fluconazole therapy. Drug reactions with eosinophilia and of systemic symptoms (DRESS) have also been made. Patients with AIDS are more likely to have severe drug-related cutaneous responses. If a rash that is thought to be caused by fluconazole appears, appears in a patient receiving treatment for a superficial fungal infection, further therapy with this agent should be stopped. Patients with systemic or invasive fungal infections should be evaluated if they get rashes.They should be closely monitored, and if bullous lesions or erythema multiforme appear, fluconazole should be stopped.

A close eye should be kept on the coadministration of fluconazole and terfenadine at doses less than 400 mg/day (see sections 4.3 Contraindications and 4.5 Interaction with other medical products and other kinds of interaction).

Similar to other azoles, anaphylaxis has been documented in rare instances. Fluconazole is one of the azoles that has been linked to aprolongation of the QT interval on the ECG. Fluconazole inhibits Rectifier Potassium, which results in QT prolongation current in the channel (Ikr).

The suppression of cytochrome P450 (CYP) 3A4 may exacerbate the QT prolongation brought on by other medications (such as amiodarone) (see section 4.5 Interaction with other medications and other forms of interaction). Following a marketing campaign,QT prolongation and torsade de pointes have very seldom occurred in patients taking fluconazole. Patients in these accounts were critically ill and had several confounding risk factors, including structural cardiac conditions, irregular electrolytes, and concurrent drug use that could have played a role. Individuals with severe heart failure and hypokalaemia are more likely to experiencefatal torsades de pointes with ventricular arrhythmias.

When treating patients with certain potentially proarrhythmic disorders, fluconazole should be used cautiously.

Patients with renal impairment should take fluconazole with caution (see section 4.2). Posology and administration technique).

Fluconazole exhibits mild inhibitory effects on CYP2C9 and CYP3A4. Additionally, fluconazole is an isoenzyme CYP2C19 inhibitor. Patients taking fluconazole who receive concurrent treatment with medications that are processed by CYP2C9, CYP2C19, and CYP3A4 and have a limited therapeutic window ought to be observed (see section 4.5 Interaction with Additional Drugs and Other Medications and other exchange).

There have been reports of persons receiving different azoles (such ketoconazole) developing adrenal insufficiency. There have also been reports of persons using fluconazole developing reversible episodes of adrenal insufficiency

Candidiasis

Research on candidiasis has revealed a rising incidence of infections caused by species other than *Candida albicans*. Some, like *C. krusei* and *C. auris*, are frequently resistant to or exhibit decreased vulnerability to *C. glabrata* fluconazole. A different antifungal medication may be necessary for certain illnesses due to failure of treatment. Prescribers are therefore encouraged to consider the frequency of resistance to fluconazole (see section 5.1 Pharmacodynamic properties) in different species of Candida.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant use of the following othermedicinal products is contraindicated:

Amiodarone: Concomitant administration of fluconazole and amiodarone may result in inhibition of amiodarone metabolism. Use of amiodarone has been linked to QT prolongation. Coadministration of fluconazole and amiodarone 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 150 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.

Terfenadine: Interaction studies have been conducted because of the incidence of severe cardiac dysrhythmias caused by lengthening of the QTc interval in patients receiving azole antifungals in addition to terfenadine. One trial using 150 mg of fluconazole per day was unable to show an extension of the QTc interval. Another trial using fluconazole dosages of 400 mg and 800 mg per day showed that coadministration of Fluconazole with Terfenadine at 400 mg/day or higher substantially raises plasma levels of terfenadine. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3 Contraindications).In the co-administration of terfenadine with fluconazole at dosages less than 400 mg/day, caution should be monitored closely.

Astemizole: Coadministration of fluconazole and astemizole may lessen clearance of Astemizole. Increased Astemizole plasma concentrations as a result may cause QT prolongation and rare cases of Torsade de Pointes. The concomitant use of astemizole and fluconazole is not recommended (see section 4.3 Contrindications).

Pimozide: Concomitant administration of fluconazole with pimozide has not been tested in vivo or in vitro. Pimozide metabolism may be inhibited as a result of coadministration of Fluconazole with Pimozide. Elevated levels of pimozide plasma cancause torsade de pointes and QT prolongation, which are uncommon conditions. Fluconazole coadministration combined with Pimozide is not recommended (see section 4.3 Contraindications).

Quinidine: Quinidine metabolism may be inhibited by concurrent administration of fluconazole and quinidine, despite the fact that this has not been investigated in vivo or in vitro. The use of quinidine has been linked to rare cases of Torsades de Pointes and QT prolongation. Fluconazole coadministration combined withquinidine is not recommended to use (see section 4.3 Contraindications).

Erythromycin: Using fluconazole and erythromycin concomitantly may raise the risk of cardiotoxicity, which can lead to abrupt cardiac death (prolonged QT interval, torsade de pointes). Fluconazole and erythromycin should not be administered concomitantly (see section 4.3 Contraindications).

Concomitant use that should be avoided

Amiodarone: Coadministration of fluconazole and amiodarone may prolong the QT interval. Caution should be observed with co-administration of amiodarone and fluconazole. If necessary,particularly with high-doseFluconazole using 800 mg.

Lemborexant: Co-administration of Fluconazole with Lemborexant increased theCmax and AUC of Lemborexant by around 1.6- and 4.2-fold respectively, which is anticipated to raise the possibility of undesirable responses, including somnolence. Avoid concomitant use of Fluconazole andLemborexant.

Effect of other drugs on Fluconazole

Cytochrome P450 (CYP) isoenzymes 2C9 and 3A4 are moderately inhibited by fluconazole. Moreover, fluconazole inhibits the isoenzyme CYP2C19. Apart from the documented/observed interactions listed below, there's a chance of higher plasma concentrations of other substances metabolized by CYP2C19, CYP2C9, and CYP3A4 in conjunction with fluconazole management. As a result, caution should be observed when using these combinations and the patients carefully monitored.
The inhibitory effect of Fluconazole lasts for four to five days after medication is stopped because of its extended half-life (see section 4.3 Contraindications).

Abrocitinib: Fluconazole (a CYP2C19, 2C9, and 3A4 inhibitor) enhanced the exposure of abrocitinib active moiety by 155%. If co-administered with fluconazole, change the dosage of abrocitinib as directed in prescription guidelines for abrocitinib.

Alfentanil: A study that was conducted after concurrent treatment with fluconazole found that there was a decrease in the clearance and distribution volume of alfentanil as well as an extension of its half-life. The inhibition of CYP3A4 by fluconazole is one potential mechanism of action. Alfentanil dosage adjustments can be required.

Nortriptyline with amitriptyline: Fluconazole enhances the effects of both medications. When starting a combination therapy, 5 nortriptyline and/or S-amitriptyline levels can be monitored and after a week. If required, the dosage of amitriptyline or nortriptyline should be changed.

Amphotericin B: When fluconazole and amphotericin B were given concurrently to infected normal and immunosuppressed mice, the following outcomes were observed: a slight additive antifungal effect against systemic *Candida albicans* infection, no interaction against intracranial *Cryptococcus neoformans* infection, and antagonistic effects of the two

medications in cases of *Aspergillus fumigatus* systemic infection.The clinical significance of the findings from these investigations is uncertain.

Anticoagulants: Fluconazole increased the prothrombin time (12%) after warfarin in an interaction study of administration in males in good health. Similar to other azole antifungals, post-marketing experience has shown that hemorrhage incidents (bruising, hematuria, melena, epistaxis, and gastrointestinal bleeding) have been documented, in correlation with increases in prothrombin time in those taking fluconazole at the same time as warfarin. When taking coumarin-type or indanedione anticoagulants, patients' prothrombin times should be closely observed. Adjustment of the dose may be necessary.

Azithromycin: A single 1150 mg oral dose of azithromycin was compared to the pharmacokinetics of a single 800 mg oral dose of fluconazole in an open-label, randomized, three-way crossover study involving eighteen healthy participants. The study also examined the effects of fluconazole on the pharmacokinetics of azithromycin. The pharmacokinetic interaction between azithromycin and fluconazole was not statistically significant.

Benzodiazepines (short-acting): After taking midazolam orally, fluconazole produced significant elevations in the psychomotor effects and midazolam concentrations. This midazolam effect seems to be more noticeable after oral fluconazole delivery than when fluconazole is given intravenously. Should concomitant benzodiazepine medication be required for patients who are on Fluconazole treatment, consideration should be given to lowering the dosage of benzodiazepines and the patients need to be well observed. Due to the inhibition of triazolam metabolism, fluconazole raises the AUC of triazolam (single dose) by about 50%, Cmax by 20% to 32%, and t½ by 25% to 50%. Hence, there may be need for triazolam dosage adjustment.

Carbamazepine: Fluconazole has been shown to impede the metabolism of carbamazepine, resulting in a 30% rise in serum levels of the drug. The possibility of carbamazepine poisoning exists.Carbamazepine dosage adjustments may be required based on concentration readings.

Calcium channel blockers: Metabolism of certain calcium channel blockers, such as nifedipine, isradipine, amlodipine, verapamil and felodipine is carried out by CYP3A4. It is possible for fluconazole to raise the systemic exposure to the calcium channels blockers. Frequent monitoring for adverse events is advised.

Celecoxib: The concurrent administration of 150 mg of celecoxib and 150 mg of fluconazole resulted in increases in the Cmax and AUC of Celecoxib by 68% and 134%, respectively. It might be necessary to take half of the celecoxib dose when administered with fluconazole.

Cyclosporin: Fluconazole considerably raises the AUC and concentration of Cyclosporin. Depending on the concentration of cyclosporin, a combination may be employed by lowering the dosage of Cyclosporin.

Cyclophosphamide: Fluconazole and cyclophosphamide coadministration produces a

rise in serum creatinine and bilirubin levels. This can be applied in cases where increased levels of serum creatinine and bilirubin is desired.

Fentanyl: A fatal case of a potential interaction between fentanyl and fluconazole was documented. The writer assessed that fentanyl overdose caused the patient's death. Moreover, in an experiment with randomized crossovers, fluconazole was found to considerably slow the clearance of fentanyl in 12 healthy volunteers. Respiratory depression may result from an elevated fentanyl concentration.

Halofantrine: Fluconazole has an inhibitory action on CYP3A4, which can lead to a rise in halofantrine plasma levels.

HMG-CoA reductase inhibitors: When fluconazole is co-administered with HMG-CoA reductase inhibitors that are metabolized through CYP3A4 (atorvastatin and simvastatin) or CYP2C9, Fluvastatin (statin metabolism reduced in the liver) (e.g., rhabdomyolysis and myopathy), the risk of these side effects increases (dose-dependently).Should concomitant treatment be required,patient needs to have regular monitoring for any signs of myopathy, rhabdomyolysis, and creatine kinase be kept under observation. Stopping HMG-CoA reductase inhibitors is advised if there is a noticeable increase in creatine kinaseor when rhabdomyolysis or myopathy is identified or suspected.Statin prescribing information may indicate the need for lower doses of HMG-CoA reductase inhibitors.

Ibrutinib: Fluconazole and other moderate CYP3A4 inhibitors increase plasma ibrutinib concentrations and may increase the risk of harm. If avoiding the combination is not possible, lower the ibrutinib dosage as directed by the ibrutinib prescribing guidelines and offer close clinical monitoring.

Ivacaftor (single or in combination with medications from the same class of therapy): An increase in exposure was observed in the transmembrane conductance regulator (CFTR) potentiator known as ivacaftor on co-administration with fluconazole.The exposure to ivacaftor was increased by three times and exposure to hydroxymethyl-ivacaftor (M1) by one and a half. A decrease in the dosage of ivacaftor (single or combination) must be followed as stated in the prescribing guidelines.

Losartan: Fluconazole the metabolism of losartan to its active metabolite, which is mostly responsible for the angiotensin II-receptor antagonistic effects that arise when losartan is taken. Patients' blood pressure needs to be continuously monitored.

Lurasidone: Fluconazole and other moderate CYP3A4 inhibitors may cause lurasidone plasma levels to rise. If it is not possible to avoid concomitant use, lower the lurasidone dosage in the prescribing information for lurasidone.

Methadone: Fluconazole may increase the serum concentration of methadone in the blood. Modification of dosage forMethadone may be required.

Non-steroidal anti-inflammatory drugs: When fluconazole was delivered in addition to flurbiprofen, the Cmax and AUC of the Flurbiprofen increased by 23% and 81%, respectively. Similarly, the Cmax and AUC of the pharmacologically active isomer-

ibuprofen[S-(+)- ibuprofen] increased by 15% and 82%, respectively, when fluconazole was given in conjunction with racemic ibuprofen (400 mg) in contrast to the drug's single administration.

Fluconazole has not been examined in detail, although it may raise the systemic exposure of other CYP2C9-metabolized non-steroidal anti-inflammatory medications (NSAIDs) including:Diclofenac, meloxicam, lornoxicam, and naproxen. Regular monitoring for harmful effects and toxicity with relation to NSAIDs is advised. There could be need for NSAID dosage adjustment.

Olaparib: Fluconazole and other moderate CYP3A4 inhibitors raise the plasma concentrations of Olaparib. In cases where concomitant use cannot be avoided it is advised to not exceed a dose of 150mg twice daily.

Oral contraceptives: Fluconazole has been used at multiple doses in two pharmacokinetic trials with a combination oral contraceptive. In the 50 mg fluconazole research, there were no discernible effects on hormone levels; however, at 150 mg daily, the AUCs of levonorgestrel and ethinyl estradiolincreased by 24% and 40%, in turn. Fluconazole at these concentrations in successive doses is therefore unlikely to impact the efficacy of combined oral contraceptive.

Phenytoin: Fluconazole prevents phenytoin from being metabolized by the liver. When co-administered, serum phenytoin concentration should be monitored to prevent phenytoin toxicity.

Prednisone: A case report said that when a 3-month course of fluconazole medication was stopped, a patient receiving prednisone for liver transplantation experienced acute adrenal cortical insufficiency. Fluconazole withdrawal most likely resulted in increased CYP3A4 activity, which raised prednisone metabolism. Individuals receiving prednisone and fluconazole for an extended period of timethe patient should be closely monitored for adrenal cortex insufficiency.

Rifabutin: It has been reported that administering fluconazole can cause an interaction concurrently with rifabutin, resulting in up to 80% higher rifabutin serum levels. Therehave been cases of uveitis in patients receiving coadministration of rifabutin with fluconazole.Careful monitoring is necessary when using fluconazole and rifabutin at the same time.

Saquinavir: Fluconazole inhibits the hepatic metabolism of saquinavir by inhibiting the co-enzyme CYP3A4 and P-glycoprotein, which raises the saquinavir's AUC by roughly 50%, Cmax by approximately 55%, and clearance of saquinavir by nearly 50%. Modification of dosage for saquinavir may be required.

Sirolimus: Fluconazole raises sirolimus plasma concentrations, possibly by inhibiting the sirolimus metabolism mediated by P-glycoprotein and CYP3A4. This combination may be used with the modification of dosage for Sirolimus based on effect/concentration data.

Sulfonyurea: Fluconazole has been demonstrated to extend in healthy individuals the serum half-life of concurrently administered oral sulfonylureas, such as tolbutamide, glibenclamide, glipizide, and chlorpropamide.It is advised to regularly check blood glucose levels and to reduce sulfonylurea dosage as needed.

Tacrolimus: Fluconazole has the potential to raise the blood levels of tacrolimus taken orally by up to five times as a result of the inhibition of tacrolimus metabolism via CYP3A4 in the intestines. Nephrotoxicity and elevated tacrolimus levels have been linked. Depending on the concentration of tacrolimus, the dosage of oral medication should be reduced.

Theophylline: Fluconazole 150 mg administered for 14 days caused an 18% reduction in the mean plasma clearance rate of theophylline in a placebo-controlled interaction study. Individuals who are at higher risk of theophylline toxicity or who are getting high doses of the drug should be monitored for indications of theophylline toxicity while on fluconazole, and the treatment course adjusted suitably if poisoning symptoms appear.

Tofacitinib: When tofacitinib is taken with other drugs,that cause CYP2C19 and CYP3A4 to be moderately inhibited (e.g., fluconazole) its exposure is enhanced. Tofacitinib dosage adjustments can be required.

Tolvaptan: Fluconazole is a moderate CYP3A4 inhibitor. When tolvaptan, a CYP3A4 substrate, is provided in combination with fluconazole, the exposure to tolvaptan is greatly enhanced (150% in AUC; 80% in Cmax). This combination increases the likelihood of major adverse effects, including considerable diuresis, dehydration, and acute kidney damage. When using tolvaptan concurrently, the dosage should be lowered and the patient handled with caution.

Vinca alkaloids: Fluconazole may raise the plasma levels of the alkaloids, although this has not been tested. (Vinblastine and vincristine, for example) and cause neurotoxicity, which may be brought on by an inhibitory action on CYP3A4.

Vitamin A: According to a case report of one patient receiving combination therapy with fluconazole and all-trans-retinoid acid, an acid form of vitamin A, adverse effects on the central nervous system (CNS) have developed in the form of pseudotumor cerebri, which went away after the medication was stopped. Although this combination may be used, the frequency of unfavourable CNS-relatedeffects need to be considered.

Voriconazole: an inhibitor of CYP2C9, CYP2C19, and CYP3A4: Oral fluconazole (400 mg on Day 1, then 150 mg Q24h for 4 days) and oral voriconazole (400 mg Q12h for 1 day, then 150 mg Q12h for 2.5 days) administered concomitantly orally to 8 healthy male volunteers increased Cmax.an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%) of voriconazole, in that order. In a subsequent clinical trial with eight fit male participants, lower dosage and/or fluconazole and voriconazole frequency did not lessen or eliminate this effect.It is not advised to take fluconazole and voriconazole at the same time, regardless of dosage.

Zidovudine: Fluconazole reduces oral zidovudine clearance by about 45%, which raises the drug's Cmax and AUC by 84% and 74%, respectively. Moreover, zidovudine's half-life was

increased by roughly 128% after fluconazole combination therapy. Individuals using this combination should be watched for the emergence of harmful zidovudine-relatedresponses. Zidovudine dosage reduction may be taken into consideration.

Studies on interactions have revealed that when meals and/or cimetidine are taken together with oral fluconazole, cimetidine, antacids or after receiving a body irradiation treatment for a bone marrow transplant, no clinically meaningful fluconazole absorption is compromised.

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

4.6 Pregnancy, Lactation, Fertility.

Pregnancy

Teratogenic Effects

Category C

Vaginal candidiasis: Use of a single 150 mg tablet

There aren't enough reliable research on fluconazole in expectant mothers.

Human data currently available do not indicate a higher incidence of congenital abnormalities after a single 150mg dose given to a pregnant mother.

Category D

Multiple dose administration

There is an unusual pattern of unique congenital abnormalities in a few published case reports for newborns exposed in utero to 400–800 mg/day of high-dose maternal fluconazole for the majority of or the entire first trimester. These observed abnormalities are similar to those observed in animalresearch. If a patient becomes pregnant while using this medication, or if this medication is administered during pregnancy the patient should be informed of the possible risk to the developing foetus.

Human Data

Numerous published epidemiologic studies indicate that low dose fluconazole exposure during pregnancy is not related with an increased risk of congenital abnormalities (most individuals obtained a single 150 mg oral dosage). A few case studies that have been released detail a unique and uncommon pattern of birth abnormalities in children whose mothers took high doses (400 to 800 mg/day) fluconazole for the majority of the first trimester in the gestational period. The characteristics observed were: brachycephaly, aberrant facial features, abnormal calvarial development, thin ribs and long bones, arthrogryposis, congenital heart, cleft palate, and femoral bowing illness. These outcomes resemble those observed in research using animals.

Animal Data
In two investigations, fluconazole was given orally to pregnant rabbits at doses of 5, 10, and 20 mg/kg and 5, 25, and 75 mg/kg, respectively, during organogenesis. Weight gain of the mother was impaired at all dosage ranges (about 0.25 to 4 times the therapeutic dose of 400 mg, according to BSA), and at 75 mg/kg (about four times the 400 mg therapeutic dose based on BSA), abortions happened. No adverse effects on the fetus were observed.

Fluconazole was given orally to pregnant rats during organogenesis in a number of trials, which resulted in higher placental weights at 25 mg/kg and impaired mother weight gain. Increases in prenatal structural variations (supernumerary) were observed at 5 and 10 mg/kg, but no foetal effects were observed. Delays in ossification, renal pelvis dilatation, and ribs were noted at 25 and 50 mg/kg and higher doses. At dosages between 80 and 320 mg/kg, (approximately two to eight times the 400 mg clinical dosage determined by BSA), the embryo-lethality of rats was elevated, and foetal defects included aberrant craniofacial ossification, cleft palate, and wavy ribs. These outcomes are consistent with the inhibition of rat estrogen production and could be the outcome of established reduced estrogeneffects on organogenesis, parturition, and pregnancy

Breastfeeding

Human milk secretes fluconazole at levels comparable to those in maternal plasma. Fluconazole should only be given to breastfeeding mothers with caution.

Fertility

When fluconazole was given orally to mice and rats for 24 months at dosages of 2.5, 5, or 10 mg/kg/day (about 2 to 7 times the recommended human dose), there was no indication that the drug had the potential to cause cancer. When given 5 and 10 mg/kg/day, male rats showed a higher frequency of hepatocellular adenomas.

In four separate mutagenicity experiments, fluconazolewith or without metabolic activationtested negative. Cytogenetic investigations conducted in vivo using mouse bone marrow cells after oral administration of fluconazoleand when fluconazole was exposed to human cells in vitro using human lymphocytes at 1000 µg/mL, no indications of chromosomal abnormalities was seen.

When given orally in dosages of 5, 10, or 20 mg/kg or parenterally in doses of 5, 25, or 75 mg/kg, fluconazole had no effect on the fertility of either male or female rats. However, the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study of rats at 5, 20, and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5 to 15 times the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the specie-specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

It is important to note that seizures or dizziness can happen occasionally when using machinery or when driving a car.

4.8 UNDESIRABLE EFFECTS

In general, fluconazole is well tolerated.
In certain patients, especially those with significant underlying illnesses like AIDS and malignancy, alterations in test findings for haematological and renal function, and abnormalities of the liver have been noted while receiving fluconazole and similar agents. However, the clinical and therapy relevance is uncertain.

Patients receiving a single Dose for Vaginal Candidiasis
Fluconazole, 150 mg administered once, was used to treat 448 patients with vaginal candidiasis in comparative clinical studies carried out in the United States. The total number of side effects that may have been caused by fluconazole were 26%. In 422 individuals receiving active comparative agents, there was a 16% incidence. The most often reported adverse events associated to therapy

Headache was reported in 13% patients treated with 150 mg of fluconazole as a single dosage for vaginitis, 7% complained of nausea, and pain in the abdomen 6%. Additional adverse effects with a frequency of 1% or more were dizziness (1%), dyspepsia (1%), diarrhea (3%), and taste perversion (1%). The majority of side effects that were recorded had mild to moderate severity. Occasionally, anaphylactic reactions and edema have been reported in marketing experience.

In Patients Receiving Multiple Doses for Other Infections

Adverse effects were reported by 16% of more than 4000 individuals who received fluconazole treatment in clinical studies lasting seven days or longer. 1.5% of patients experienced adverse clinical events that resulted in treatment discontinuation, while 1.3% of patients experienced abnormal laboratory test results. Patients with HIV reported clinical adverse events more frequently (21%) than those without the virus(13% HIV-Negative patients. Yet, the trends in HIV-positive and negative infections were similar. The percentages of patients who stop their treatment because of clinical adverse events (1.5%) were comparable across the two groups.

In clinical studies, 4048 individuals taking fluconazole for seven or more days experienced the following treatment-related clinical adverse effects at an incidence of 1% or higher: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal discomfort 1.7%, and diarrhea1.5%.

Rare instances of severe hepatic responses have been reported in both clinical trials and marketing experience while taking fluconazole. These hepatic reactions have ranged in severity from mild, momentary increases in transaminases to cholestasis and clinical hepatitisand fulminant hepatic failure, including mortalities. Examples of hepatic responses

that were deadly were seen to mostly affect individuals with severe underlying medical disorders (often AIDS or cancer) and frequently when taking several concurrent drugs. Hepatitis and jaundice are examples of transient hepatic responses that have happenedin individuals without any further discernible risk factors. Each time under these situations, liver function went back to baseline after stopping the fluconazole.

A statistically significant rise in median AST (SGOT) levels was noted in two comparative trials assessing the effectiveness of fluconazole for the prevention of cryptococcal meningitis relapse. In one trial, the baseline value was 30 IU/L; in the other, it was 34 IU/L to 66 IU/L. The frequency of over eight times the normal level of serum transaminase increases overall

Fluconazole-treated patients in clinical trials had an overall rate of blood transaminase increases of more than 8 times the upper limit of normal of about 1%. These increases happened in people with serious underlying illnesses, mainly AIDS or

cancers, the majority of whom were taking numerous concurrent drugs, including as many known to be hepatotoxic. The frequency of serum transaminases that are excessively increased was higher in those taking fluconazole together with one or more of the following drugs concomitantly: valproic acid, isoniazid, phenytoin, rifampin, or oral sulfonylurea hypoglycaemia agents.

Post-marketing Experience

Additionally, during the post-marketing experience, the following unfavorable incidents have happened;

Immunologic: Anaphylaxis, encompassing facial edema, pruritus, and angioedema, has been documented in a small number of patients.

Whole Body: Asthenia, exhaustion, fever, and malaise.

Cardiovascular: Torsade de Pointes and QT prolongation.

Central Nervous System: vertigo, seizures.

Hematopoietic and Lymphatic: Leukopenia, encompassing agranulocytosis and neutropenia,

thrombocytopenia.

Metabolic: elevated triglyceridemia, hypokalemia, and cholesterol.

Gastrointestinal: Cholestasis, dry mouth, hepatocellular damage, dyspepsia, vomiting.

Other Senses: Taste perversion.

Musculoskeletal System: myalgia.

Nervous System: Insomnia, paresthesia, somnolence, tremor, vertigo.

Skin and Appendages: Acute generalized exanthematous-pustulosis, drug eruption, increased sweating, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis alopecia.

Adverse Events in Children

Adverse event patterns and laboratory abnormalities observed in the clinical trials of children are similar to adult patterns in terms of frequency and pattern.

A total of 1,616 days of fluconazole treatment at doses up to 15 mg/kg/day were given to 577 paediatric patients, ages 1 day to 17 years, as part of Phase II/III clinical trials carried out in the United States and Europe. Adverse events due to therapy occurred in 13% of children.

The most often reported symptoms were nausea (3%), vomiting (5%), and abdominal discomfort (3%)as well as diarrhea (2%). Two percent of patients had their treatment stopped because of negative clinical events and in 1.4% of patients as a result of anomalies in laboratory tests. Most of the laboratory abnormalities associated with therapy included elevated transaminases or alkaline phosphatase.

Percentage of Patients with Treatment-Related Side Effects

	FLUCONAZOLE (N=577)	COMPARATIVE AGENTS (N=451)
With any side effect	13.0	9.3
Vomiting	5.4	5.1
Abdominal Pain	2.8	1.6
Nausea	2.3	1.6
Diarrhea	2.1	2.2

4.9 OVERDOSE

Fluconazole overdoses that result in hallucinations and paranoid behaviour have been documented.

If an overdose occurs, supportive measures and gastrointestinal symptomatic therapy Lavage should be started if clinically indicated.

Urine is the main excretory form of fluconazole. Three hours of haemodialysis reduces plasma levels by around 50%.

When extremely high dosages of fluconazole were administered to mice and rats, the clinical outcomes in both species included ptosis, reduced respiration and motility, salivation, lacrimation, and urinarycyanosis, incontinence, and lack of the righting reflex; clonicseizures occasionally preceded death.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: triazole derivatives, antimycotics for systemic use.

Mechanism of action

Triazole antifungal drug fluconazole is a strong and targeted inhibitor of fungal sterol production. The main mechanism of action is the inhibition of 14-alpha-lanosterol mediated demethylation, mediated by fungal cytochrome P-450a critical stage in the formation of fungal ergosterol. A build-up of 14-alpha-methyl results in the subsequent loss of ergosterol in the fungal cell membrane and may be accountable for fluconazole's antifungal properties. It has been demonstrated that fluconazole is more specific for fungal cytochrome P-450 enzymescompared to different mammalian cytochrome P-450 enzyme systems.

In healthy male volunteers, there is no clinically significant difference in the response to adrenocorticotropic hormone (ACTH) stimulation or endogenous steroid levels when fluconazole 150 mg to 400 mg is taken daily.

Pharmacokinetic/pharmacodynamic relationship

Minimum inhibitory concentration (MIC) values and efficacy against experimental mycoses caused by Candida spp. are correlated in animal investigations. Clinical research demonstrates an approximately 1:1 linear correlation between the fluconazole dose and the AUC. Additionally, there is a direct but insufficient relationship between an oral candidosis patient's successful clinical response and the AUC or dosage, and a lesser degree of candidemia to therapy. In a similar vein, infections caused by strains having a greater Fluconazole Minimum Inhibitory Control have a less likely cure.

Microbiology

Fluconazole exhibits antifungal efficacy in vitro against species of clinically prevalent Candida, such as *C. albicans*, *C. parapsilosis*, and *C. tropicalis*. *C. glabrata* exhibits decreased fluconazole susceptibility. Conversely, *C. krusei* has an innate resistance to fluconazole.

Lately,*C. auris*, an emerging species, has a tendency to be somewhat resistant to fluconazole.

Additionally, fluconazole shows action against *Cryptococcus neoformans* and*Cryptococcusgattii*in vitro as well as to the endemic moulds *Paracoccidioides brasiliensis*, *Histoplasma capsulatum*, *Coccidioides immitis,* and *Blastomyces dermatiditis*.

Fluconazole taken orally or intravenously demonstrated efficacy in multiple animal models of fungal infection. Evidence of activity has been shown against opportunistic mycoses, such as infections caused by Candida spp., which can include systemic candidiasis in animals with impaired immune systems; *C. neoformans*, which might include intracranial infections; those involving Trichophyton spp. and Microsporum spp.

Moreover, fluconazole has been demonstrated to be active in animal models of endemic mycoses, such as infections with *Blastomyces dermatitidis,* along with *Coccidioides immitis*, which can cause cerebral infections and with *Histoplasma capsulatum* in both immunocompromised and healthy animals.

Mechanism of resistance

The most frequent mechanism of resistance found in generally susceptible species of Candida involves the target azole enzymes, which are in charge of ergosterol production. The target enzyme is encoded by the gene (ERG11), and point mutations in this gene change the target with decreased azole affinity. The overexpression of ERG11 causes the generation of elevated target enzyme concentrations, necessitating higher intracellular drug concentrations to inhibit every molecule of the target enzyme present in the cell.

The active efflux of fluconazole out of the cell via the activation of two different types of multidrug efflux transporters (the main facilitators), which are represented by MDR genes, and those of the ATP-binding cassette superfamily, which are encoded by CDR genesrepresents the second major mechanism of drug resistance.

Fluconazole resistance results by upregulating the MDR gene, but upregulation of the CDR genescould result in resistance to other azoles.

In *Candida glabrata*, resistance is typically accompanied by overexpression of CDR genes, which confers resistance to other azoles.

Superinfections with Candida species other than Candida albicans have been reported; these species frequently exhibit decreased susceptibility (C. glabrata) or resistance to fluconazole (e.g*., C. krusei,C. auris*). Such infections may need a different kind of antifungal medication.

5.2 Pharmacokinetic properties

Fluconazole has identical pharmacokinetic characteristics whether taken orally or intravenously.Fluconazole is well absorbed when taken orally, and its plasma levels (as well as its systemic bioavailability) reach levelsabove 90% than when taken intravenously. The process of oral absorption is not impacted by concurrent meal consumption. When fasting, peak plasma concentrations happen between0.5- and 1.5-hourspost-dose, with a roughly 30-hour plasma elimination half-life

Plasma doses and concentrations are proportional. By Days 4 to 5, 90% steady-state levels are attained with multiple once-daily doses. When a loading dosage of twice the regular daily dose is administered (on Day 1), plasma levels can on day 2, rise to roughly 90% steady-state values. Apparent volume of distribution for Fluconazole approximates to total body water (TBW). The Plasma protein binding is only 11%–12%.Fluconazole penetrates all bodily fluids examined. Salivary fluconazole levels as well as sputum and plasma levels are comparable.

In individuals with fungal meningitis, fluconazole levels in thecerebrospinal fluid (CSF) are approximately 80% the corresponding plasma levels. Majority of the drug is excreted through the kidneys, approximately 80% of the dose is excreted as unchanged in the urine. The clearance of fluconazole and creatinine are proportional. No evidence of circulating metabolites is present.

The rationale for vaginal candidiasis single-dose therapy is the long plasma elimination half-life. doses of once per day and once per week for other indications.

A pharmacokinetic study was conducted on ten nursing women who had either temporarily or permanently quit breastfeeding. The study assessed the levels of fluconazole in the breast milk and plasma 48 hours after a single 150 mg dosage of Fluconazole. On average, the amount of fluconazole found in breast milk was approximately 98% of what was found in maternal plasma. Peak average breast milk production concentration at 5.2 hours after dosing was 2.61 mg/L.

Pharmacokinetics in children

Pharmacokinetic data for children has been included in Table 2 as follows:

Table 2: Pharmacokinetic properties

Age	**Dose (mg/kg)**	**Half-life (Hours)**	**AUC (µg.h/ml)**
11days - 11months	Single-IV 3 mg/kg	23.0	110.1
9months – 13 years	Single-Oral 2 mg/kg	25.0	94.7
9 months- 13 years	Single-Oral 8 mg/kg	19.5	362.5
5 years-15 years	Multiple-IV 2 mg/kg	17.4*	67.4*
5 years-15 years	Multiple-IV 4 mg/kg	15.2*	139.1*
5 years-15 years	Multiple-IV 8 mg/kg	17.6*	196.7*
Mean age 7 years	Multiple-Oral 3 mg/kg	15.5	41.6

*Denotes final day

Throughout their stay in the intensive care unit, premature neonates (gestational age about 28 weeks) received intravenous fluconazole injections every third day at a maximum dose of 6 mg/kg. On Day 1, the average half-life (hours) was 74 (range 44–185), decreased over time to a mean of 53 on Days 7 (range 30-131) and 47 on Days 13 (range 27-68).

On the first day, the AUC (µg.h/ml) was 271 (range 173-385) and increased to a mean of 490 (range 292-734). On Day 7 it gave a mean of 292 (range 167-566) and on Day 13 a mean of 360 (range 167-566) decrease.

At Day 1, the volume of distribution (ml/kg) was 1183 (range 1070-1470). Over time, it climbed to a mean of Day 7 at 1184 (range 510-2130) and Day 13 at 1328 (range 1040-1680).

Pharmacokinetics in Elderly

Twenty-two patients 65 years of age or older who received a single oral dose of 50 mg of fluconazole participated in a pharmacokinetic study. Diuretics were being taken concurrently by ten of these individuals. The Cmaxoccured 1.3 hours after the injection at a dose of 1.54µg/ml. AUC averaged 76.4 ± 20.3 µg.h/mland 46.2 hours was the mean terminal half-life. The values of these pharmacokinetic parameters are greater compared to analogue values recorded for healthy young male participants. Diuretic coadministration did not substantially change the Cmax or AUC.

Furthermore, compared to younger volunteers, the elderly had poorer creatinine clearance (74 ml/min), a higher percentage of medication recovered unchanged in urine (22%) and renal clearance estimates (0.124 ml/min/kg) for fluconazole. Therefore, the reduced renal function in the elderly appears to be associated with changes in the disposition of fluconazole, characteristic of this group. Plotting the terminal elimination half-life of each participant vs creatinine clearance in relation to the predicted half-life-creatinine clearance curve derived from healthy individuals and individuals with varying levels of renal insufficiency revealed that 21 out of 22 individuals were in the estimated half-life-creatinine clearance curves of 95% confidence interval.

These findings support the theory that the reduced kidney function seen in the elderly patients relative to normal young male volunteers account for the higher values in the pharmacokinetic parameter expected in older people.

5.3 Preclinical safety Data

Carcinogenesis

When administered orally to mice and rats for a duration of 24 months at doses of 2.5, 5 or 10 mg/kg/day (about 2-7 times the authorized human dose), fluconazole did not exhibit any signs of carcinogenic risk.Hepatocellular adenomas were more common in male rats treated with 5 and 10 mg/kg/day.

Mutagenesis

Fluconazole was found to be non-mutagenic in assays for mutagenicity in four strains of *Salmonella typhimurium* and in the mouse lymphoma L5178Y system, regardless of metabolic activation. In vivo Cytogenetic Studies (mouse bone marrow cells, after fluconazole is taken orally) and in vitro (human lymphocytes exposed to fluconazole at 1000 µg/ml), did not exhibit any signs of chromosomal abnormalities.

Impairment of Fertility

When given orally in dosages of 5 mg/kg, 10 mg/kg, or 20 mg/kg, or parenterally in doses of 5 mg/kg, 25 mg/kg, or 75 mg/kg, fluconazole had no effect on the fertility of either male or female rats. However, at the onset of oral doses of 20 mg/kg, parturition was somewhat delayed.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Capsule content:

Lactose monohydrate

Maize starch

Colloidal silica dioxide

Magnesium stearate

Sodium lauryl sulfate

Capsule shell composition:

150 mg capsules

Gelatin Titanium dioxide (E171))

Erythrosin (E127))

Indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

Keep out of the sight and reach of children.

Do not use FLUCONAZOLE after the expiry date which is stated on the Carton/Blister after expiration. The expiry date refers to the last day of that month.

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

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Hard gelatin capsules

150 mg light blue cap and white opaque body, marked with the Emzor logo and Fluconazole 150mg blister packs of 10.

6.6. Special precautions for disposal and other handling

Capsules should be swallowed whole.

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

7. MARKETING AUTHORISATION HOLDER

Emzorpharmaceuticals Limited Flowergate mixed scheme, KM1, Sagamu/Benin Expressway, Ogun State, Nigeria.

8. PRESCRIPTION STATUS

Prescription only medicine