Summary of Product Characteristics

1. Name of the Finished Pharmaceutical product

Fluconazole Infusion BP (2 mg/mL) - Syszol

1.1 Strength

Not Applicable

1.2 Pharmaceutical form

Solution for Infusion

2. Qualitative and quantitative composition

Each ml of Solution for Infusion contains 2 mg of Fluconazole.
Excipient(s) with known effect
Each ml of Solution for Infusion contains 0.15 mmol (3.5 mg) sodium (as chloride)
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for Infusion

4. Clinical particulars

4.1 Therapeutic indications

Treatment
Fluconazole Infusion BP (2 mg/mL) is indicated for the treatment of:
1. Oropharyngeal and esophageal candidiasis.
Fluconazole Infusion BP (2 mg/mL) is also effective for the treatment of serious systemic candidal infections, including urinary tract infection, peritonitis, and pneumonia.
2. Cryptococcal meningitis.
3. Prevention of the recurrence of cryptococcal meningitis in patients with acquired immunodeficiency syndrome (AIDS). Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.
Prophylaxis
Fluconazole Infusion BP (2 mg/mL) is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or

radiation therapy.

4.2 Posology and method of administration

Method of Administration

Recommended dosages in adults and children

Loading Dose
Administration of a loading dose on the first day of treatment, consisting of twice the usual daily dose, results in plasma concentrations close to steady state by the second day.
Patients with acute infections should be given a loading dose equal to twice the daily dose, not to exceed a maximum single dose of 400 mg in adults or 12 mg/kg in children, on the first day of treatment.
Dosage Equivalency Scheme

Pediatric Patients	Adults
3 mg/kg	100 mg
6 mg/kg	200 mg
12 mg/kg*	400 mg

* Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

Recommended Treatment Guidelines		
Indication	Adults	C
Oropharyngeal Candidiasis	100 mg once daily for at least 2 weeks to decrease the likelihood of relapse.	3 mg/kg once daily for at least 2 weeks to
Esophageal Candidiasis	100 mg to 200 mg once daily for a minimum of 3 weeks, and for at least 2 weeks following resolution of symptoms.	3 mg/kg to 6 mg/kg once daily for a minimum of 3 weeks, and for at least 2

Systemic Candidiasis (Candidemia and Disseminated Candidal Infections)	200 mg to 400 mg once daily for a minimum of 4 weeks, and for at least 2 weeks following resolution of symptoms.	6 mg/kg to 12 mg/kg per day have been used in an open, non-
Cryptococcal Meningitis	200 mg to 400 mg once daily. The duration of therapy for cryptococcal meningitis is unknown, it is recommended that the initial therapy should last a minimum of 10 weeks.	6 mg/kg to 12 mg/kg once daily. The recommended duration for initial therapy is
Prevention of Recurrence of Cryptococcal Meningitis in Patients with AIDS	200 mg once daily.	6 mg/kg once daily.

Premature neonates

Experience with Fluconazole Infusion BP (2 mg/mL) in neonates is limited to pharmacokinetic studies in premature newborns. Based upon the prolonged half-life seen in premature newborns (gestation age 26 to 29 weeks), these children, in the first two weeks of life, should receive the same dosage (mg/kg) as in older children, but administered every 72 hours. After the first 2 weeks, these children should be dosed once daily.

Neonates

No information regarding Fluconazole Infusion BP (2 mg/mL) pharmacokinetics in full-term newborns is available.

Prophylaxis in adult patients

The recommended Fluconazole Infusion BP (2 mg/mL) daily dosage for the prevention of candidiasis in adult patients undergoing bone marrow transplantation is 400 mg once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils/mm) should start Fluconazole Infusion BP (2 mg/mL) prophylaxis several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells/mm.

The intravenous infusion of Fluconazole Infusion BP (2 mg/mL) should be administered at a maximum rate of approximately 200 mg/hour given as a continuous infusion.

Dosage in patients with impaired renal function

Adults
Fluconazole is cleared primarily by renal excretion as unchanged drug. In patients with impaired renal function, an initial loading dose of 50 mg to 400 mg should be given (for children, see below). After the loading dose, the daily dose (according to indication) should be administered as outlined in the following table:

D		
Creatinine Clearance (mL/min)	Creatinine Clearance (mL/sec)	Recommended Dose (%)
> 50	> 0.83	100
21-50 (no dialysis)	0.35-0.83 (no dialysis)	50
11-20 (no dialysis)	0.18-0.34 (no dialysis)	25
Hemodialysis	Hemodialysis	100 after each

Patients on hemodialysis should receive 100% of the recommended dose after each hemodialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance.
When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance.
Children
Although the pharmacokinetics of fluconazole have not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults. The following formula may be used to estimate creatinine clearance in children:

$$\frac{K \times \text{linear length or height (cm)}}{\text{serum creatinine (mg/100 mL)}}$$

(Where K=0.55 for children older than 1 year and 0.45 for infants.)

Intravenous administration
Fluconazole Infusion BP (2 mg/mL) is well absorbed and excreted predominantly unchanged in urine following intravenous administration in humans. Peak plasma concentrations after intravenous administration are attained rapidly, usually within 2 hours of dosing. The terminal plasma elimination half-life is approximately 30 hours (range 20-50 hours). The daily dose of Fluconazole Infusion BP (2 mg/mL) and the route of administration should be based on the infecting organism, the patient's condition and the response to therapy. Treatment should be continued until clinical parameters and laboratory tests indicate that an active fungal infection has been cured or has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

4.3 Contraindications

Fluconazole Infusion BP (2 mg/mL) is contraindicated in patients who have shown hypersensitivity to fluconazole, to any of its excipients or to related azole compounds.
Co-administration of drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as erythromycin, pimozide and quinidine are contraindicated in patients receiving fluconazole.

4.4 Special warnings and precautions for use

Fluconazole should be administered with caution to patients with liver dysfunction. Hepatic injury: Fluconazole Infusion BP (2 mg/mL) 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 the patient has been observed.
Fluconazole hepatotoxicity has usually, but not always been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during Fluconazole Infusion BP (2 mg/mL) therapy should be monitored for the development of more severe hepatic injury. Fluconazole Infusion BP (2 mg/mL) should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole.
Fluconazole should be administered with caution to patients with renal dysfunction (see Dosage and Administration- Impaired Renal Function).
Adrenal insufficiency has been reported in patients receiving other azoles (e.g., ketoconazole).

Reversible cases of adrenal insufficiency were reported in patients while receiving fluconazole or when fluconazole was discontinued.
Anaphylaxis: In rare cases, anaphylaxis has been reported.
Dermatologic: Patients have rarely developed exfoliative skin disorders during treatment with Fluconazole Infusion BP (2 mg/mL). In patients with serious underlying diseases (predominantly AIDS and malignancy), those have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with Fluconazole Infusion BP (2 mg/mL) should be monitored closely and the drug discontinued if lesions progress.
QT Prolongation
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on an 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. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular arrhythmias and torsades de pointes. The potential for proarrhythmic events increases with co- administration of other drugs that prolong the QT interval such as some antiarrhythmics, antihistamines, psychotropic agents and antibacterials. Caution and careful monitoring should be used with concomitant administration of such drugs.

Fluconazole should be administered with caution to patients with proarrhythmic conditions.

CYP2C9, CYP2C19 and CYP3A4 metabolized drugs

Fluconazole is a moderate CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of the isoenzyme CYP2C19. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP 3A4 should be monitored.

Use in Nursing Mothers

Fluconazole is secreted in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

Use in Children

An open-label, randomized, controlled trial has shown Fluconazole Infusion BP (2 mg/mL) to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age.

In a non-comparative study of children with serious systemic fungal infections, Fluconazole Infusion BP (2 mg/mL) was effective in the treatment of candidemia (10 of 11 patients cured) and disseminated candidiasis (5 of 6 patients cured or improved).

Fluconazole Infusion BP (2 mg/mL) was effective for the suppression of cryptococcal meningitis and/or disseminated cryptococcal infection in a group of 6 children treated in a compassionate study of Fluconazole Infusion BP (2 mg/mL) for the treatment of life-threatening or serious mycosis. There is no information regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children.

In addition, the use of Fluconazole Infusion BP (2 mg/mL) in children with cryptococcal meningitis, candidal esophagitis or systemic candidal infections is consistent with the approved use of Fluconazole Infusion BP (2 mg/mL) in similar indications for adults, and is supported by pharmacokinetic studies in children establishing dose proportionality between children and adults.

The safety of Fluconazole Infusion BP (2 mg/mL) in children has been established in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1616 days.

Efficacy of Fluconazole Infusion BP (2 mg/mL) has not been established in infants less than 6 months of age. A small number of patients (29) ranging in age from 1 day to 6 months have been treated safely with Fluconazole Infusion BP (2 mg/mL). Use in Elderly

Fluconazole Infusion BP (2 mg/mL) was well tolerated by patients aged 65 years and over.

Fluconazole is primarily cleared by renal excretion as unchanged drug. Because elderly patients are more likely to have decreased renal function, caution should be exercised and dose adjusted based on creatinine clearance. It may be useful to monitor renal function.

In a small number of elderly patients with bone marrow transplant (BMT) in which Fluconazole Infusion BP (2 mg/mL) was administered prophylactically there was a greater incidence of drug discontinuation due to adverse reactions (4.3%) than in younger patients (1.7%).

Use in Patients with Hereditary Problems

Effects on Ability to Drive and Use Machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

Superinfections

Development of resistance to fluconazole has not been studied; however, there have been reports of cases of superinfection 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.

As for other anti-infectives used prophylactically, prudent medical practice dictates that Fluconazole Infusion BP (2 mg/mL) be used judiciously in prophylaxis, in view of the theoretical risk of emergence of resistant strains.

Paediatric Population

Not available

4.5 Interaction with other medicinal products and other forms of interaction

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also a strong inhibitor of the isoenzyme CYP2C19. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 coadministered 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.
Clinically or potentially significant drug interactions between fluconazole and the following agents/classes have been observed:
Alfentanil Amiodarone, Amitriptyline/Nortriptyline, Amphotericin B, Azithromycin, Benzodiazepines, (Short Acting), Carbamazepine, Calcium Channel Blockers, Celecoxib, Cimetidine, Coumarin-Type or Indanedione Anticoagulants, Cyclosporine, Cyclophosphamide, Drugs prolonging QTc interval: Pimozide, Quinidine, Erythromycin Fentanyl, Halofantrine, HMG-CoA reductase inhibitors Hydrochlorothiazide, Ibrutinib Losartan Methadone, Non-steroidal anti-inflammatory drugs: Olaparib, Oral Contraceptives Oral Hypoglycemics Phenytoin Prednisone Rifabutin, Rifampin, Saquinavir, Sirolimus, Sulfonylureas, Tacrolimus, Theophylline, Tofacitinib, Tolvaptan, Triazolam, Vinca Alkaloids, Vitamin A, Zidovudine, Voriconazole (CYP2C9, CYP2C19 and CYP3A4 Inhibitors), Alfentanil.

Additional information on special populations

Not available

Paediatric population

Not available

4.6 Fertility, Pregnancy and Lactation

Fluconazole Infusion BP (2 mg/mL) should not be used in pregnant women except in patients with severe or potentially life-threatening fungal infections in whom Fluconazole Infusion BP (2 mg/mL) may be used if the anticipated benefit outweighs the possible risk to the fetus.
If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the foetus.

Use in Women of Child-bearing Potential
Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period with Fluconazole Infusion BP (2 mg/mL) and for approximately 1 week (5 to 6 half-lives) after the final dose

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 UNDESIRABLE EFFECTS) while taking Fluconazole and should be advised not to drive or

operate machines if any of these symptoms occur.

4.8 Undesirable effects

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 adverse reactions 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	Common	Uncommon	Rare
Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
Immune system disorders			Anaphylaxis
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
Psychiatric disorders		Somnolence, insomnia	
Nervous system disorders	Headache	Seizures, dizziness, paraesthesia, taste perversion	Tremor
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			*Torsade de pointes,* QT prolongation
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation dyspepsia, flatulence, dry mouth	
Hepatobiliary disorders	Alanine aminotransferase Increased, aspartate aminotransferase Increased, blood alkaline phosphatase increased	Cholestasis, jaundice, bilirubin increased	Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage

Skin and subcutaneous tissue disorders	Rash	Drug eruption, urticarial, increased, increased sweating	Toxic epidermal necrolysis, Stevens-Johnson Syndrome, acute generalised exanthematouspu stulosis, dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal and connective tissue and bone disorders		Myalgia	
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever	

Paediatric Population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Symptoms: There have been reports of overdosage with Fluconazole Infusion BP (2 mg/mL) (fluconazole) accompanied by hallucination and paranoid behaviour.

Treatment: In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Fluconazole is largely excreted in urine. A 3-hour hemodialysis session decreases plasma levels by approximately 50%.

Mice and rats receiving very high doses of fluconazole, whether orally or intravenously, displayed a variety of nonspecific, agonal signs such as decreased activity, ataxia, shallow respiration, ptosis, lacrimation, salivation, urinary incontinence and cyanosis. Death was sometimes preceded by clonic convulsions.

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 hemodialysis session decreases plasma levels by approximately 50%.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives

ATC-code: J02AC01

Mode of action

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14-α-demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14-α-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

5.2 Pharmacokinetic Properties

Fluconazole is a polar bis-triazole antifungal drug. Studies have shown that fluconazole exhibits specificity as an inhibitor of the fungal as opposed to mammalian cytochrome P-450 mediated reactions, including those involved in steroid biosynthesis and drug metabolism. Many of the clinical advantages of Fluconazole Infusion BP (2 mg/mL) are a result of its unique pharmacokinetic properties.

HUMAN
Adults
Absorption
The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes and do not appear to be affected by gastric pH. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Essentially all of the administered drug reaches systemic circulation; thus, there is no evidence of first-pass metabolism of the drug. In addition, no adjustment in dosage is necessary when changing from p.o. to i.v. or vice versa.
Peak plasma concentrations (C_{max}) in fasted normal volunteers occur rapidly following oral administration, usually between 1 and 2 hours of dosing with a terminal plasma elimination half- life of approximately 30 hours (range 20-50 hours) after oral administration. The long plasma elimination half-life provides the

basis for once daily dosing with Fluconazole in the treatment of fungal infections.

In fasted normal volunteers, administration of a single oral 400 mg dose of Fluconazole leads to a mean Cmax of 6.72 µg/mL (range: 4.12 to 8.08 µg/mL) and after single oral doses of 50-400 mg, fluconazole plasma concentrations and AUC (area under the plasma concentration-time curve) are dose proportional.

Steady-state concentrations are reached within 5-10 days following oral doses of 50-400 mg given once daily. Administration of a loading dose on the first day of treatment of twice the usual daily dose results in plasma concentrations close to steady state by the second day.

Pharmacokinetics in Children

In children, pharmacokinetic data {MEAN (% cv)} have been reported as follows:

Pharmacokinetic Data in Children					
Age Studied	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (Hours)	Cmax (µg/mL)	V d
9 Months - 13 years	Single - Oral 2 mg/kg	0.40 (38%) N = 14	25.0	2.9 (22%) N = 16	-
9 Months - 13 years	Single - Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N = 15	-
5 - 15 years	Multiple i.v. 2 mg/kg	0.49 (40%) N = 4	17.4	5.5 (25%) N = 5	0.722 (36%)
5 - 15 years	Multiple i.v. 4 mg/kg	0.59 (64%) N = 5	15.2	11.4 (44%) N = 6	0.729 (33%)
5 - 15 years	Multiple i.v. 8 mg/kg	0.66 (31%) N = 7	17.6	14.1 (22%) N = 8	1.069 (37%)

Clearance corrected for body weight was not affected by age in these studies. Mean body clearance in adults is reported to be 0.23 mL/min/kg (17%).

In premature newborns (gestation age 26 to 29 weeks), the mean (% cv) clearance within 36 hours of birth was 0.180 mL/min/kg (35%, N = 7), which increased with time to a mean of 0.218 mL/min/kg (31%, N=9) six days later and 0.333 mL/min/kg (56%, N = 4) 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later.

The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients:

Pediatric Patients	Adults
3 mg/kg	100 mg
6 mg/kg	200 mg
12 mg/kg*	400 mg

* Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

Pharmacokinetics in Lactating Women

A pharmacokinetic study in 10 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 fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98% of that measured in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose, similar to that observed in maternal plasma (2.61 mg/L at 2.6 hours post-dose) and the elimination half-life from breast milk approximates the plasma elimination half-life of 30 hours.

Distribution

The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11%-12%) and is constant over the concentration range tested (0.1 mg/L to 10 mg/L). This degree of protein binding is not clinically meaningful. Following either single- or multiple-oral doses for up to 14 days, fluconazole penetrates into all body tissues and fluids studied. In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations regardless of dose, route, or duration of dosing.

In patients with bronchiectasis, sputum concentrations of fluconazole following a single 150 mg oral dose were equal to plasma concentrations at both 4 and 24 hours post dose.

In patients with fungal meningitis, fluconazole concentrations in the CSF (cerebrospinal fluid) are approximately 80% of the corresponding plasma concentrations. Whole blood concentrations of fluconazole indicated that the drug freely enters erythrocytes and maintains a concentration equivalent to that of plasma.

Metabolism and Excretion

Fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Following administration of radiolabeled fluconazole, greater than 90% of the radioactivity is excreted in the urine. Approximately 11% of the radioactivity in urine is due to metabolites. An additional 2% of the total radioactivity is excreted in feces.

The pharmacokinetics of fluconazole do not appear to be affected by age alone but are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of fluconazole may need to be reduced in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

QT Prolongation

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 .

Pharmacodynamics

The effects of fluconazole on the metabolism of carbohydrates, lipids, adrenal and gonadal hormones were assessed. Fluconazole appears to have no clinically significant effects on carbohydrate or lipid metabolism in man. In normal volunteers, fluconazole administration (doses ranging from 200 mg to 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the adrenocorticotropic hormone (ACTH)-stimulated cortisol response.

In all species and man: (1) Cmax levels are similar after normalization for different body mass, (2) volume of distribution is about 0.8 L/kg, (3) plasma protein binding is in the range of 11-12% and (4) bioavailability is greater than 80%.

Plasma concentrations of fluconazole generally declined in a monophasic manner with first order kinetics. The elimination half-life ranges from about 2 to 5 hours in the mouse to approximately 30 hours in man (range 20-50 hours).

The longer elimination half-life in man is a consequence of low plasma clearance (0.28 mL/min/kg) relative to the normal glomerular filtration rate (1.8 mL/min/kg).

5.3 Preclinical safety data

Carcinogenesis:

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

In reproduction toxicity studies in rat an increased incidence of hydronephrosis and extension of renal pelvis was reported and embryonal lethality was increased. An increase in anatomical variations and delayed ossification was noted as well as prolonged delivery and dystocia. In reproduction toxicity studies in rabbits abortions were recorded.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Chloride BP
Water for Injections
BP

6.2 Incompatibilities

It is recommended that Fluconazole Infusion (2 mg/mL) for intravenous infusion be infused separately.

6.3 Shelf life

24 Months from the date of manufacturing

6.4 Special precautions for storage

It should be stored at a temperature not exceeding 30°C. It should not be refrigerated or allowed to freeze. .

6.5 Nature and contents of container

Syszol is available as 100 mL in Non PVC Bag.

6.6 Special precautions for disposal and other handling

The containers are for single use only.
Discard any unused portion.
Do not reconnect partially used containers.

7. Marketing authorisation holder & Manufacturing site address

Otsuka Pharmaceutical India Private Limited Survey No.199 to 201 & 208 to 210,
Village – Vasana –
Chacharwadi, Tal- Sanand,
Dist: Ahmedabad – 382 213, India.

8. Marketing authorisation number(s)

H2025/CTD11663/24565

9. Date of first registration/ renewal of the registration

2025 March 06

10. Date of revision of the text

21/08/2026