For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

SYSCAN

1. Generic Name

Fluconazole Infusion B.P.

2. Qualitative and quantitative Composition:

Each 100 ml bottle contains:

Fluconazole I.P.	200 mg
Sodium Chloride I.P.	0.9 gm
Water for Injection I.P.	q.s.

3. Dosage form and strength

Dosage form: Intravenous Infusion

Strength: 200mg/100ml

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of systemic candidiasis, mucosal candidasis and cryptococcosis and prevention of fungal infections in patients with malignancy.

4.2 Posology and method of administration

Posology

For Adults

Multiple Dose

Since oral absorption is rapid and almost complete, the daily dose of fluconazole is the same for oral and intravenous administration. In general, a loading dose of twice the daily dose is recommended on the first day of therapy to result in plasma concentrations close to steady-state by the second day of therapy.

The daily dose of fluconazole for the treatment of infections other than vaginal candidiasis should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection 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.

Oropharyngeal candidiasis:

The recommended dosage of fluconazole for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of oropharyngeal candidiasis generally resolves within several days, but treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

Esophageal candidiasis:

The recommended dosage of fluconazole for esophageal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.

Systemic Candida infections:

For systemic Candida infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used.

Urinary tract infections and peritonitis:

For the treatment of Candida urinary tract infections and peritonitis, daily doses of 50 to 200 mg have been used in open, non-comparative studies of small numbers of patients.

Cryptococcal meningitis:

The recommended dosage for treatment of acute cryptococcal meningitis is 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after the cerebrospinal fluid becomes culture negative. The recommended dosage of fluconazole for suppression of relapse of cryptococcal meningitis in patients with AIDS is 200 mg once daily.

Prophylaxis in patients undergoing bone marrow transplantation:

The recommended fluconazole daily dosage for the prevention of candidiasis in patients undergoing bone marrow transplantation is 400 mg, once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils cells/mm^3) should start fluconazole prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells/mm^3.

For Children

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.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature new borns. Based on the prolonged half-life seen in premature new borns (gestational 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 two weeks, these children should be dosed once daily.

y. No information regarding fluconazole pharmacokinetics in full-term new borns is available.

Oropharyngeal candidiasis:

The recommended dosage of fluconazole for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.

Esophageal candidiasis:

For the treatment of esophageal candidiasis, the recommended dosage of fluconazole in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/day may be used, based on medical judgment of the patient's response to therapy. Patients with esophageal candidiasis should be treated for a minimum of three weeks and for at least 2 weeks following the resolution of symptoms.

Systemic Candida infections:

For the treatment of candidemia and disseminated *Candida* infections, daily doses of 6 to 12 mg/kg/day have been used in an open, non-comparative study of a small number of children.

Cryptococcal meningitis:

For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of 12 mg/kg once daily may be used, based on medical judgment of the patient's response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of fluconazole is 6 mg/kg once daily.

Dosage in Patients With Impaired Renal Function

Fluconazole is cleared primarily by renal excretion as unchanged drug. In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50 mg to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance (mL/min)	**Recommended Dose (%)**
>50	100
< 50 (no dialysis)	50
Hemodialysis	100% after each hemodialysis

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.

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.

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 in adults:

Males: $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$

Females: 0.85 × above value

Although the pharmacokinetics of fluconazole has 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:

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

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

Method of administration

Fluconazole Injection, may be administered by intravenous infusion. Fluconazole Injection, has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of Fluconazole Injection, should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion.

Fluconazole Injection, in glass and plastic containers are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if the solution is cloudy or precipitated or if the seal is not intact.

Directions for IV Use of Fluconazole in Plastic Containers:

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

COMPATIBILITY OF INTRAVENOUS INFUSION:

Although further dilution is unnecessary it is compatible with following fluids:

A. Dextrose 20%
B. Ringer's solution
C. Hartmann's solution
D. Potassium chloride in dextrose
E. Normal saline

Mixing with any other drug prior to infusion is not recommended.

4.3 Contraindications

Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles. Co-administration of other 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

Hepatic injury:

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

Anaphylaxis:

In rare cases, anaphylaxis has been reported.

Dermatologic:

Exfoliative skin disorders during treatment with fluconazole have been reported. Fatal outcomes have been reported in patients with serious underlying diseases. Patients with deep seated fungal infections who develop rashes during treatment with fluconazole should be monitored closely and the drug discontinued if lesions progress. Fluconazole should be discontinued in patients treated for superficial fungal infection who develop a rash that may be attributed to fluconazole.

Potential for fetal harm:

There are no adequate and well-controlled clinical trials of fluconazole in pregnant women. Case reports describe a pattern of distinct congenital anomalies in infants exposed *in utero* to high dose maternal fluconazole (400 to 800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. If fluconazole 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 fetus. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with fluconazole 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials.

PRECAUTIONS

General

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. During post marketing surveillance, there have been rare cases of QT prolongation and torsade

de pointes in patients taking fluconazole. Most of these reports involved 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 torsade de pointes.

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

Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsade de pointes) and consequently sudden heart death. This combination should be avoided.

Fluconazole should be administered with caution to patients with renal dysfunction.

Adrenal insufficiency has been reported in patients receiving azoles, including fluconazole. Reversible cases of adrenal insufficiency have been reported in patients receiving fluconazole.

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

4.5 Drugs interactions

Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Patients treated with fluconazole, who are also concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9 and CYP3A4, should be monitored for adverse reactions associated with the concomitantly administered drugs. 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 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 to 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 and are described in greater detail below:

Abrocitinib: Drug interaction studies indicate that when co-administered with fluconazole (strong inhibitor of CYP2C19; moderate inhibitor of CYP2C9, CYP3A4), the systemic exposure of abrocitinib and its active metabolites increased. Avoid concomitant use of abrocitinib with fluconazole. Refer to the abrocitinib prescribing Information for additional details.

Alfentanil: A study observed a reduction in clearance and distribution volume as well as prolongation of t½ 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.

Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of fluconazole and amiodarone is necessary, notably with high-dose fluconazole (800 mg).

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 1 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 *Candida 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.

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.

Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil, 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.

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.

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

Coumarin-type anticoagulants: Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Careful monitoring of prothrombin time in patients receiving fluconazole and coumarin-type anticoagulants is recommended. Dose adjustment of warfarin may be necessary.

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.

Cyclosporine: Fluconazole significantly increases cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving fluconazole and cyclosporine. This combination may be used by reducing the dosage of cyclosporine depending on cyclosporine concentration.

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 12 healthy volunteers, it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is co-administered with HMG-CoA reductase inhibitors metabolized 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.

Hydrochlorothiazide: In a pharmacokinetic interaction study, coadministration 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.

Ibrutinib: Moderate inhibitors of CYP3A4 such as fluconazole may increase plasma ibrutinib concentrations and increase risk of adverse reactions associated with ibrutinib. If ibrutinib and fluconazole are concomitantly administered, reduce the dose of ibrutinib as instructed in ibrutinib prescribing information and the patient should be frequently monitored for any adverse reactions associated with ibrutinib.

Lemborexant: Concomitant administration of fluconazole increased Lemborexant Cmax and AUC by approximately 1.6- and 4.2- fold, respectively, which was expected to increase risk of adverse reactions, such as somnolence. Avoid concomitant use of fluconazole with Lemborexant.

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

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

Non-steroidal anti-inflammatory drugs: The Cmax and AUC of flurbiprofen were increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] were 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 non-steroidal anti-inflammatory drugs (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.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, reduce the dose of olaparib as instructed in the LYNPARZA® (Olaparib) Prescribing Information.

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

Oral hypoglycemics: Clinically significant hypoglycemia may be precipitated by the use of fluconazole with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined fluconazole and glyburide use. Fluconazole reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When fluconazole is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary.

Phenytoin: Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving fluconazole and phenytoin is recommended.

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.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a 3 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.

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and quinidine is contraindicated.

Rifabutin: There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

Rifampin: Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of fluconazole when it is administered with rifampin.

Saquinavir: Fluconazole increases the AUC of saquinavir by approximately 50%, Cmax by approximately 55%, and decreases the clearance of saquinavir by approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of Pglycoprotein. Dosage adjustment of saquinavir may be necessary.

Short-acting benzodiazepines: 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 short-acting benzodiazepines, which are metabolized by the cytochrome P450 system, are concomitantly administered with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

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

Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Theophylline: Fluconazole increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving fluconazole and theophylline is recommended.

Tofacitinib: Systemic exposure to tofacitinib is increased when tofacitinib is coadministered with fluconazole. Reduce the dose of tofacitinib when given concomitantly with fluconazole (i.e., from 5 mg twice daily to 5 mg once daily as instructed in the XELJANZ® [tofacitinib] label).

Triazolam: Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, Cmax by 20% to 32%, and increases t½ by 25% to 50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

Tolvaptan: Plasma exposure to tolvaptan is significantly increased (200% in AUC; 80% in Cmax) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor. This interaction may result in the risk of a significant increase in adverse reactions associated with tolvaptan, particularly significant diuresis, dehydration and acute renal failure. If tolvaptan and fluconazole are concomitantly administered, the tolvaptan dose should be reduced as instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.

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 alltrans-retinoid acid (an acid form of vitamin A) and fluconazole, central nervous system (CNS) related undesirable effects have developed in the form of pseudotumor 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: Avoid concomitant administration of voriconazole and fluconazole. Monitoring for adverse events and toxicity related to voriconazole is recommended; especially, if voriconazole is started within 24 h after the last dose of fluconazole.

Zidovudine: Fluconazole increases the Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approximately 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.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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

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

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg or with parenteral doses of 5 mg/kg, 25 mg/kg, or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study in rats at 5 mg/kg, 20 mg/kg, 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 species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

Teratogenic Effects.

Potential for Fetal Harm: Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. A few published case reports describe a pattern of distinct congenital anomalies in infants exposed *in utero* to high dose maternal fluconazole (400 to 800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with fluconazole 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. If fluconazole 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 fetus.

Spontaneous abortions and congenital abnormalities have been suggested as potential risks associated with 150 mg of fluconazole as a single or repeated dose in the first trimester of pregnancy based on retrospective epidemiological studies. There are no adequate and well-controlled studies of fluconazole in pregnant women.

Human Data

Case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These effects are similar to those seen in animal studies.

Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials.

Animal Data

Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies at doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg and at 5 mg/kg, 25 mg/kg, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels

(approximately 0.25 to 4 times the 400 mg clinical dose based on body surface area [BSA] comparison), and abortions occurred at 75 mg/kg (approximately 4 times the 400 mg clinical dose based on BSA); no adverse fetal effects were observed.

In several studies in which pregnant rats received fluconazole orally during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 to 320 mg/kg (approximately 2 to 8 times the 400 mg clinical dose based on BSA), embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis, and parturition.

Nursing Mothers

Fluconazole was present in low levels in breast milk following administration of a single 150 mg dose, based on data from a study in 10 breastfeeding women who temporarily or permanently discontinued breastfeeding 5 days to 19 months postpartum. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 mL/kg/day) based on the mean peak milk concentration (2.61 mcg/mL [range: 1.57 to 3.65 mcg/mL] at 5.2 hours post-dose) was 0.39 mg/kg/day, which is approximately 13% of the recommended pediatric dose for oropharyngeal candidiasis. (Labeled pediatric dose is 6 mg/kg/day on the first day followed by 3 mg/kg/day; estimated infant dose is 13% of 3 mg/kg/day maintenance dose). There are no data on fluconazole levels in milk after repeated use or after high-dose fluconazole.

Pediatric Use

An open-label, randomized, controlled trial has shown fluconazole to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age.

The use of fluconazole in children with cryptococcal meningitis, *Candida* esophagitis, or systemic *Candida* infections is supported by the efficacy shown for these indications in adults and by the results from several small noncomparative pediatric clinical studies. In addition, pharmacokinetic studies in children have established a dose proportionality between children and adults.

In a noncomparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of fluconazole was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 13/15 (87%) of evaluable

patients had a mycologic cure at the end of treatment but two of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

The efficacy of fluconazole for the suppression of cryptococcal meningitis was successful in 4 of 5 children treated in a compassionate-use study of fluconazole 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.

The safety profile of fluconazole in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1,616 days.

Efficacy of fluconazole 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.

Geriatric Use

In non-AIDS patients, side effects possibly related to fluconazole treatment were reported in fewer patients aged 65 and older (9%, n=339) than for younger patients (14%, n=2240). However, there was no consistent difference between the older and younger patients with respect to individual side effects. Of the most frequently reported (>1%) side effects, rash, vomiting, and diarrhea occurred in greater proportions of older patients. Similar proportions of older patients (2.4%) and younger patients (1.5%) discontinued fluconazole therapy because of side effects. In post-marketing experience, spontaneous reports of anemia and acute renal failure were more frequent among patients 65 years of age or older than in those between 12 and 65 years of age. Because of the voluntary nature of the reports and the natural increase in the incidence of anemia and renal failure in the elderly, it is however not possible to establish a causal relationship to drug exposure.

Controlled clinical trials of fluconazole did not include sufficient numbers of patients aged 65 and older to evaluate whether they respond differently from younger patients in each indication. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

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

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

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.

In Patients Receiving Multiple Doses for Other Infections

Sixteen percent of over 4000 patients treated with fluconazole in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving fluconazole for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

Hepato-biliary: In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with fluconazole. The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of fluconazole.

In two comparative trials evaluating the efficacy of fluconazole for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Post-Marketing Experience

In addition, the following adverse events have occurred during post-marketing experience.

Immunologic: In rare cases, anaphylaxis (including angioedema, face edema and pruritus) has been reported.

Body as a Whole: Asthenia, fatigue, fever, malaise.

Cardiovascular: QT prolongation, torsade de pointes.

Central Nervous System: Seizures, dizziness.

Hematopoietic and *Lymphatic:* Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

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 including fixed drug eruption, increased sweating, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), alopecia, Hyperpigmentation.

Adverse Reactions in Children

The pattern and incidence of adverse events and laboratory abnormalities recorded during pediatric clinical trials are comparabl

e to those seen in adults.

In Phase II/III clinical trials conducted in the United States and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with fluconazole at doses up to 15 mg/kg/day for up to 1,616 days. Thirteen percent of children experienced treatmentrelated adverse events. The most commonly reported events were vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Treatment was discontinued in 2.3% of patients due to adverse clinical events and in 1.4% of patients due to laboratory test abnormalities. The majority of treatment-related laboratory abnormalities were elevations of 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

Description of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting by reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

There have been reports of overdose with fluconazole accompanied by hallucination and paranoid behavior.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted.

Fluconazole is largely excreted in urine. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

In mice and rats receiving very high doses of fluconazole, clinical effects in both species included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex, and cyanosis; death was sometimes preceded by clonic convulsions.

5 Pharmacological properties

5.1 Mechanism of Action

Fluconazole is a highly selective inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-α-demethylase. This enzyme functions to convert lanosterol to ergosterol. 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. Mammalian cell demethylation is much less sensitive to fluconazole inhibition.

5.2 Pharmacodynamic properties

Resistance

A potential for development of resistance to fluconazole is well known. Fungal isolates exhibiting reduced susceptibility to other azoles may also show reduced susceptibility to fluconazole. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known.

Fluconazole resistance may arise from a modification in the quality or quantity of the target enzyme (lanosterol 14-α-demethylase), reduced access to the drug target, or some combination of these mechanisms.

Point mutations in the gene (*ERG11*) encoding for the target enzyme lead to an altered target with decreased affinity for azoles. Overexpression of *ERG11* results in the production of high concentrations of the target enzyme, creating the need for higher intracellular drug concentrations to inhibit all of the enzyme molecules in the cell.

The second major mechanism of drug resistance involves active efflux of fluconazole out of the cell through the activation of two types of multidrug efflux transporters; the major facilitators (encoded by *MDR* genes) and those of the ATP-binding cassette superfamily (encoded by *CDR* genes). Upregulation of the *MDR* gene leads to fluconazole resistance, whereas, upregulation of *CDR* genes may lead to resistance to multiple azoles.

Resistance in *Candida glabrata* usually includes upregulation of *CDR* genes resulting in resistance to multiple azoles. For an isolate where the minimum inhibitory concentration (MIC) is categorized as Intermediate (16 to 32 mcg/mL), the highest fluconazole dose is recommended.

Candida krusei should be considered to be resistant to fluconazole. Resistance in *C. krusei* appears to be mediated by reduced sensitivity of the target enzyme to inhibition by the agent.

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.

Antimicrobial Activity

Fluconazole has been shown to be active against most isolates of the following microorganisms **both *in vitro* and in clinical infections.**

Candida albicans

Candida glabrata (Many isolates are intermediately susceptible)

Candida parapsilosis

Candida tropicalis

Cryptococcus neoformans

The following *in vitro* data are available, **but their clinical significance is unknown.**

At least 90% of the following fungi exhibit an *in vitro* MIC less than or equal to the susceptible breakpoint for fluconazole (https://www.fda.gov/STIC) against isolates of similar genus or organism group. However, the effectiveness of fluconazole in treating clinical infections due to these fungi has not been established in adequate and well controlled clinical trials.

Candida dubliniensis

Candida guilliermondii

Candida kefyr

Candida lusitaniae

Candida krusei should be considered to be resistant to fluconazole. Resistance in *C. krusei* appears to be mediated by reduced sensitivity of the target enzyme to inhibition by the agent.

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.

5.3 Pharmacokinetic properties

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration.

Peak plasma concentrations (C_{max}) in fasted normal volunteers occur between one and two hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20 to 50 hours) after oral administration.

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

Steady-state concentrations are reached within 5 to 10 days following oral doses of 50 to 400 mg given once daily. Administration of a loading dose (on Day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11 to 12%). Following either single or multiple oral doses for up to 14 days, fluconazole penetrates into all body fluids studied (see table below). 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 cerebrospinal fluid (CSF) are approximately 80% of the corresponding plasma concentrations.

A single oral 150 mg dose of fluconazole administered to 27 patients penetrated into vaginal tissue, resulting in tissue:plasma ratios ranging from 0.94 to 1.14 over the first 48 hours following dosing.

A single oral 150 mg dose of fluconazole administered to 14 patients penetrated into vaginal fluid, resulting in fluid:plasma ratios ranging from 0.36 to 0.71 over the first 72 hours following dosing.

Tissue or Fluid	**Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration***
Cerebrospinal fluid[#]	0.5 – 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4 – 0.7

* Relative to concurrent concentrations in plasma in subjects with normal renal function.

[#] Independent of degree of meningeal inflammation.

In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

The pharmacokinetics of fluconazole 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. A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

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.

Pharmacokinetics in Children

In children, the following pharmacokinetic data {Mean (%cv)} have been reported:

Age Studied	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (Hours)	C_{max} (mcg/mL)	Vd_{ss} (L/kg)
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 IV 2 mg/kg	0.49 (40%) N=4	17.4	5.5 (25%) N=5	0.722 (36%) N=4
5-15 years	Multiple IV 4 mg/kg	0.59 (64%) N=5	15.2	11.4 (44%) N=6	0.729 (33%) N=5
5-15 years	Multiple IV 8 mg/kg	0.66 (31%) N=7	17.6	14.1 (22%) N=8	1.069 (37%) N=7

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

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

Pharmacokinetics in Elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 mcg/mL and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 mcg•h/mL, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Co administration of diuretics did not significantly alter the AUC or C_{max}. In addition, creatinine clearance (74 mL/min), the percent of drug recovered unchanged in urine (0 to 24 hours, 22%), and the fluconazole renal clearance estimates (0.124 mL/min/kg) for the elderly were generally lower than those of younger volunteers.

Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristic of this group. A plot of each subject's terminal elimination half-life versus creatinine clearance compared to the predicted half-life – creatinine clearance curve derived from normal subjects and subjects with varying degrees of renal insufficiency indicated that 21 of 22 subjects fell within the 95% confidence limit of the predicted half-life – creatinine clearance curves. These results are consistent with the hypothesis that higher values for the pharmacokinetic parameters observed in the elderly subjects compared to normal young male volunteers are due to the decreased kidney function that is expected in the elderly.

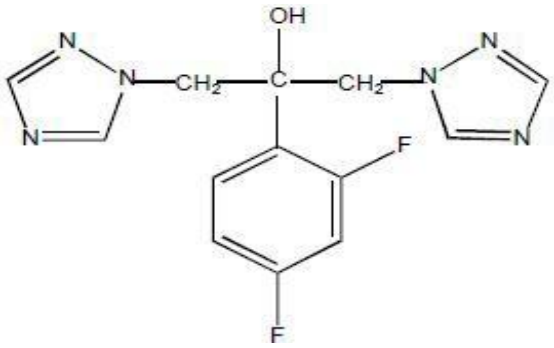
6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

NA

7 Description

Fluconazole is 2,4-difluoro-,a.a.-[1]-bis (1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol with an empirical formula of $C_{13}H_{12}F_2N_6O$ and molecular weight 306.3. The structural formula is:



8 Pharmaceutical particulars

8.1 Incompatibilities

Although further dilution is unnecessary it is compatible with following fluids:

F. Dextrose 20%
G. Ringer's solution
H. Hartmann's solution
I. Potassium chloride in dextrose
J. Normal saline

Mixing with any other drug prior to infusion is not recommended.

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

It is available as intravenous infusion of Fluconazole I.P. as 2 mg/ml in bottle of 100 ml.

It is available as sterile non-pyrogenic, isotonic, single dose container.

8.4 Storage and handing instructions

Store at a temperature not exceeding 25^{o}C, Do not freeze.

The infusion does not contain any preservatives. It is for single use only.

Discard any remaining solution after use.

Protect from light on removal from manufacturer's original carton.

9 Patient Counselling Information

Package leaflet: Information for the user

SYSCAN

Fluconazole Infusion B.P.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

9.1 What SYSCAN is and what it is used for

Fluconazole is 2,4-difluoro-,a.a.-[1]-bis (1H-1,2,4-triazol-1-ylmethyl)benzyl alcohol.

It is used for the treatment of systemic candidiasis, mucosal candidasis and cryptococcosis and prevention of fungal infections in patients with malignancy.

9.2 What you need to know before you take SYSCAN

Do not take SYSCAN

Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding crosshypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles. Coadministration of other 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.

Warnings and precautions

Hepatic injury:

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

Anaphylaxis:

In rare cases, anaphylaxis has been reported.

Dermatologic:

Exfoliative skin disorders during treatment with fluconazole have beenreported. Fatal outcomes have been reported in patients with serious underlying diseases. Patients with deep seated fungal infections who develop rashes during treatment with fluconazole should be monitored closely and the drug discontinued if lesions progress. Fluconazole should be discontinued in patients treated for superficial fungal infection who develop a rash that may be attributed to fluconazole.

Potential for fetal harm:

There are no adequate and well-controlled clinical trials offluconazole in pregnant women. Case reports describe a pattern of distinct congenital anomalies in infants exposed *in utero* to high dose maternal fluconazole (400 to 800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. If fluconazole 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 fetus. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with fluconazole 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials.

PRECAUTIONS

General

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. During postmarketing surveillance, there have been rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. Most of these reports involved 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 torsade de pointes.

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

Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsade de pointes) and consequently sudden heart death. This combination should be avoided.

Fluconazole should be administered with caution to patients with renal dysfunction.

Adrenal insufficiency has been reported in patients receiving azoles, including fluconazole. Reversible cases of adrenal insufficiency have been reported in patients receiving fluconazole.

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

Pregnancy, breast-feeding and fertility

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

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

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg or with parenteral doses of 5 mg/kg, 25 mg/kg, or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study in rats at 5 mg/kg, 20 mg/kg, 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 species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

<u>Teratogenic Effects.</u>

Potential for Fetal Harm: Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. A few published case reports describe a pattern of distinct congenital anomalies in infants exposed *in utero* to high dose maternal fluconazole (400 to 800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with fluconazole 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. If fluconazole 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 fetus.

Spontaneous abortions and congenital abnormalities have been suggested as potential risks associated with 150 mg of fluconazole as a single or repeated dose in the first trimester of pregnancy based on retrospective epidemiological studies. There are no adequate and well-controlled studies of fluconazole in pregnant women.

Human Data

Case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These effects are similar to those seen in animal studies.

Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials.

Animal Data

Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies at doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg and at 5 mg/kg, 25 mg/kg, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels

(approximately 0.25 to 4 times the 400 mg clinical dose based on body surface area [BSA] comparison), and abortions occurred at 75 mg/kg (approximately 4 times the 400 mg clinical dose based on BSA); no adverse fetal effects were observed.

In several studies in which pregnant rats received fluconazole orally during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 to 320 mg/kg (approximately 2 to 8 times the 400 mg clinical dose based on BSA), embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis, and parturition.

Nursing Mothers

Fluconazole was present in low levels in breast milk following administration of a single 150 mg dose, based on data from a study in 10 breastfeeding women who temporarily or permanently discontinued breastfeeding 5 days to 19 months postpartum. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 mL/kg/day) based on the mean peak milk concentration (2.61 mcg/mL [range: 1.57 to 3.65 mcg/mL] at 5.2 hours post-dose) was 0.39 mg/kg/day, which is approximately 13% of the recommended pediatric dose for oropharyngeal candidiasis. (Labeled pediatric dose is 6 mg/kg/day on the first day followed by 3 mg/kg/day; estimated infant dose is 13% of 3 mg/kg/day maintenance dose). There are no data on fluconazole levels in milk after repeated use or after high-dose fluconazole

Driving and using machines

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

9.3 How to use SYSCAN

Fluconazole Injection, may be administered by intravenous infusion. Fluconazole Injection, has been used safely for up to fourteen days of intravenous therapy. The intravenous infusion of Fluconazole Injection, should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion.

Fluconazole Injection, in glass and plastic containers are intended only for intravenous administration using sterile equipment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if the solution is cloudy or precipitated or if the seal is not intact.

Directions for IV Use of Fluconazole in Plastic Containers:

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

9.4 Possible side 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.

In Patients Receiving Multiple Doses for Other Infections

Sixteen percent of over 4000 patients treated with fluconazole in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving fluconazole for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

Hepato-biliary: In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with fluconazole. The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred

among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of fluconazole.

In two comparative trials evaluating the efficacy of fluconazole for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking fluconazole concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Post-Marketing Experience

In addition, the following adverse events have occurred during post-marketing experience.

Immunologic: In rare cases, anaphylaxis (including angioedema, face edema and pruritus) has been reported.

Body as a Whole: Asthenia, fatigue, fever, malaise.

Cardiovascular: QT prolongation, torsade de pointes.

Central Nervous System: Seizures, dizziness.

Hematopoietic and *Lymphatic:* Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

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 including fixed drug eruption, increased sweating, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), alopecia, Hyperpigmentation.

Adverse Reactions in Children

The pattern and incidence of adverse events and laboratory abnormalities recorded during pediatric clinical trials are comparabl

e to those seen in adults.

In Phase II/III clinical trials conducted in the United States and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with fluconazole at doses up to 15 mg/kg/day for up to 1,616 days. Thirteen percent of children experienced treatmentrelated adverse events. The most commonly reported events were vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Treatment was discontinued in 2.3% of patients due to adverse clinical

events and in 1.4% of patients due to laboratory test abnormalities. The majority of treatment-related laboratory abnormalities were elevations of 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

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting by reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store SYSCAN

Store at a temperature not exceeding 25ºC, Do not freeze.

The infusion does not contain any preservatives. It is for single use only.

Discard any remaining solution after use.

Protect from light on removal from manufacturer's original carton.

9.6 Contents of the pack and other information

It is available as intravenous infusion of Fluconazole I.P. as 2 mg/ml in bottle of 100 ml.

It is available as sterile non-pyrogenic, isotonic, single dose container.

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

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IN/SYSCAN INFUSION 200mg/100ml/Nov 2022/05/PI