



Fungone[®] (Fluconazole)

1. NAME OF THE PRODUCT

Fungone[®] (Fluconazole) 150mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fungone[®] 150mg Capsules

Each capsule contains:

Fluconazole USP.....150mg

3. PHARMACEUTICAL FORM

Capsule

Appearance: White colored granules in hard gelatin capsule having maroon colored shell, “***Fungone***[®] 150mg” printed on cap and “” printed three times on the body.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Fungone[®] is indicated in adults for the treatment of:

- Cryptococcal meningitis.
- Coccidioidomycosis.
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.
- Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.
- Candidal balanitis when local therapy is not appropriate.
- Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal candida infections when systemic therapy is indicated.
- Tinea unguinum (onychomycosis) when other agents are not considered appropriate.

Fungone[®] is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.



- To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year).
- Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Haematopoietic Stem Cell Transplantation).

***Fungone*[®] is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old:**

Fungone[®] is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. *Fungone*[®] can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence.

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.

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing 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.

Adults:

Indications		Posology	Duration of treatment
Cryptococcosis	Treatment of cryptococcal meningitis.	Loading dose: 400mg on Day 1 Subsequent dose: 200mg to 400mg once daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800mg
	Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.	200mg once daily	Indefinitely at a daily dose of 200mg



Coccidioidomycosis		200mg to 400mg once daily	11 months up to 24 months or longer depending on the patient. 800mg daily may be considered for some infections and especially for meningeal disease
Invasive candidiasis		Loading dose: 800mg on Day 1 Subsequent dose: 400mg once daily	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	Oropharyngeal candidiasis	Loading dose: 200mg to 400mg on Day 1 Subsequent dose: 100mg to 200mg once daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	Oesophageal candidiasis	Loading dose: 200mg to 400mg on Day 1 Subsequent dose: 100mg to 200mg once daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	Candiduria	200mg to 400mg once daily	7 to 21 days. Longer periods may be used in patients with severely



			compromised immune function.
	Chronic atrophic candidiasis	50mg once daily	14 days
	Chronic mucocutaneous candidiasis	50mg to 100mg once daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromise and infection
Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse	Oropharyngeal candidiasis	100mg to 200mg once daily or 200mg 3 times per week	An indefinite period for patients with chronic immune suppression
	Oesophageal candidiasis	100mg to 200mg once daily or 200mg 3 times per week	An indefinite period for patients with chronic immune suppression
Genital candidiasis	Acute vaginal candidiasis	150mg	Single dose
	Candidal balanitis		
	Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year).	150mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150mg once weekly maintenance dose	Maintenance dose: 6 months.
Dermatomycosis	tinea pedis, tinea corporis, tinea cruris, <i>candida</i> infections	150mg once weekly or 50mg once daily	2 to 4 weeks, tinea pedis may require treatment for up to 6 weeks
	tinea versicolor	300mg to 400mg once weekly	1 to 3 weeks
		50mg once daily	2 to 4 weeks



	tinea unguium (onychomycosis)	150mg once weekly	Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally requires 3 to 6 months and 6 to 12 months, respectively. However, growth rates may vary widely in individuals, and by age. After successful treatment of long- term chronic infections, nails occasionally remain disfigured.
Prophylaxis of candidal infections in patients with prolonged neutropaenia		200mg to 400mg once daily	Treatment should start several days before the anticipated onset of neutropaenia and continue for 7 days after recovery from neutropaenia after the neutrophil count rises above 1000 cells per mm ³

Special populations:

Elderly: Dosage should be adjusted based on the renal function.

Renal impairment: *Fungone*[®] is predominantly excreted in the urine as unchanged active substance.

No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of *Fungone*[®], an initial dose of 50mg to 400mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:



Creatinine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no haemodialysis)	50%
Haemodialysis	100% after each haemodialysis

Patients on haemodialysis should receive 100% of the recommended dose after each haemodialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance.

Hepatic impairment: Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction.

Paediatric population:

A maximum dose of 400mg daily should not be exceeded in paediatric population. As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. **Fungone®** is administered as a single daily dose. The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for “Term newborn infants” who often exhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

Indication	Posology	Recommendations
Mucosal candidiasis	Initial dose: 6mg/kg Subsequent dose: 3mg/kg once daily	Initial dose may be used on the first day to achieve steady state levels more rapidly
Invasive candidiasis Cryptococcal meningitis	Dose: 6 to 12mg/kg once daily	Depending on the severity of the disease
Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 6mg/kg once daily	Depending on the severity of the disease
Prophylaxis of <i>Candida</i> in immunocompromised patients	Dose: 3 to 12mg/kg once daily	Depending on the extent and duration of the induced neutropenia

Adolescents (from 12 to 17 years old): Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher **Fungone®** clearance than observed for adults. A dose of 100, 200 and 400mg in adults corresponds to a 3, 6 and 12mg/kg dose in children to obtain a comparable systemic exposure. Safety and efficacy for genital candidiasis indication in paediatric population has not been established. If treatment for genital candidiasis is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adults posology.



Term newborn infants (0 to 27 days): Neonates excrete fluconazole slowly. There are few pharmacokinetic data to support this posology in term newborn infants.

Age group	Posology	Recommendations
Term newborn infants (0 to 14 days)	The same mg/kg dose as for infants, toddlers and children should be given every 72 hours	A maximum dose of 12mg/kg every 72 hours should not be exceeded
Term newborn infants (from 15 to 27 days)	The same mg/kg dose as for infants, toddlers and children should be given every 48 hours	A maximum dose of 12mg/kg every 48 hours should not be exceeded

Method of administration:

For oral use only.

The physician should prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. The capsule formulation is not adapted for use in infants and small children.

Do not chew or crush capsule.

The capsules should be swallowed whole with water and independent of food intake.

4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substance, to related azole substances, or to any of the excipients
- Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400mg per day or higher based upon results of a multiple dose interaction study.
- Co-administration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide quinidine and erythromycin are contraindicated in patients receiving fluconazole.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Tinea capitis: Fluconazole has been studied for treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Fluconazole should not be used for *tinea capitis*.

Cryptococcosis: The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.



Candidiasis: Studies have shown an increasing prevalence of infections with *Candida* species other than *C. albicans*. These are often inherently resistant (e.g. *C. krusei* and *C. auris*) or show reduced susceptibility to fluconazole (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various *Candida* species to fluconazole.

Deep endemic mycoses: The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as *paracoccidioidomycosis*, *lymphocutaneous sporotrichosis* and *histoplasmosis* is limited, which prevents specific dosing recommendations.

Renal system: Fluconazole should be administered with caution to patients with renal dysfunction.

Adrenal insufficiency: Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with prednisone.

Hepatobiliary system: Fluconazole should be administered with caution to patients with liver dysfunction. Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury. The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Cardiovascular system: Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (I_{kr}). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades 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 treatment that may have been contributory. Patients with hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and torsades de pointes. Fluconazole should be administered with caution to patients with potentially proarrhythmic conditions. Co-administration of other medicinal



products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated.

Halofantrine: Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended.

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

Hypersensitivity: In rare cases anaphylaxis has been reported.

Cytochrome P450: Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored.

Terfenadine: The co-administration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored.

Excipients: This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. Concomitant treatment with fluconazole and Cisapride is contraindicated.

Terfenadine: The combined use of fluconazole at doses of 400mg or greater with terfenadine is contraindicated. The co-administration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsades de pointes. Co-administration of fluconazole and astemizole is contraindicated.



Pimozide: Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsades de pointes. Co-administration of fluconazole and pimozide is contraindicated.

Quinidine: Use of quinidine has been associated with QT prolongation and rare occurrences of torsades de pointes. Co-administration of fluconazole and quinidine is contraindicated.

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. Co-administration of fluconazole and erythromycin is contraindicated.

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

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. This combination should be avoided.

Concomitant use that should be used with caution:

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 (800mg).

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

The effect of other medicinal products on fluconazole

Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and a 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered. Interaction studies have shown that when oral fluconazole is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Hydrochlorothiazide: Co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.

The effect of fluconazole on other medicinal products:

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolised by



CYP2C9, CYP2C19 and CYP3A4 co-administered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4- 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.

Abrocitinib: Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If co-administered with fluconazole, adjust the dose of abrocitinib as instructed in the abrocitinib prescribing information.

Alfentanil: Dose adjustment of alfentanil may be necessary.

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

Amphotericine B: Limited non-clinical studies have shown variable pharmacodynamic interactions between fluconazole and amphotericin B. The clinical relevance of these findings has not been established.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melaena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200mg and midazolam 7.5mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200mg daily given concurrently with triazolam 0.25mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

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

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.

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

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases (dose-dependent) when fluconazole is co-administered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.

Ibrutinib: Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib to 280mg once daily (two capsules) for the duration of the inhibitor use and provide close clinical monitoring.

Ivacaftor (alone or combined with drugs in the same therapeutic class): Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

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



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

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

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

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose 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. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

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

Lurasidone: Moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.

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

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

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200mg fluconazole and 250mg



phenytoin intravenously, caused an increase of the phenytoin AUC₂₄ by 75% and C_{min} by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

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

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

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P- glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide). Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during co-administration.

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

Tofacitinib: Exposure of tofacitinib is increased when tofacitinib is co-administered with medications that result in both moderate inhibition of CYP3A4 and strong inhibition of CYP2C19 (e.g., fluconazole). Therefore, it is recommended to reduce tofacitinib dose to 5mg once daily when it is combined with these drugs.

Tolvaptan: Exposure to tolvaptan is significantly increased (200% in AUC; 80% in C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, 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: This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Co-administration of oral voriconazole (400mg Q12h for 1 day, then 200mg Q12h for 2.5 days) and oral fluconazole (400mg on day 1, then 200mg Q24h for 4 days) resulted in an increase in C_{max} and AUC of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

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

Azithromycin: There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

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

4.6. FERTILITY, PREGNANCY AND LACTATION:

Women of childbearing potential: Before initiating treatment, the patient should be informed of the potential risk to the foetus. After single dose treatment, a washout period of 1 week (corresponding to 5-6 half-lives) is recommended before becoming pregnant. For longer courses of treatment, contraception may be considered, as appropriate, in women of childbearing potential throughout the treatment period and for 1 week after the final dose.

Fertility: Fluconazole did not affect the fertility of male or female rats.

Pregnancy: Observational studies suggest an increased risk of spontaneous abortion in women treated with fluconazole during the first and/or second trimester compared to women not treated with fluconazole or treated with topical azoles during the same period. Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered



in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses $\leq 450\text{mg}$ compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450mg fluconazole. Available epidemiological studies on cardiac malformations with use of fluconazole during pregnancy provide inconsistent results. However, a meta-analysis of 5 observational studies including several thousand pregnant women exposed to fluconazole during the first trimester finds a 1.8-2 fold increased risk of cardiac malformations when compared to no fluconazole use and/or topical azoles use. Case reports describe a pattern of birth defects among infants whose mothers received high-dose (400 to 800mg/day) fluconazole during pregnancy for 3 months or more, in the treatment of coccidioidomycosis. The birth defects seen in these infants include brachycephaly, ears dysplasia, giant anterior fontanelles, femoral bowing and radio-humeral synostosis. A causal relationship between fluconazole use and these birth defects is uncertain. Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary. Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

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

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 while taking Fluconazole and should be advised not to drive or operate machines if any of these symptoms occur.

4.8. UNDESIRABLE EFFECTS:

The adverse reactions ranked under headings of system organ class and frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $<$



1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment.

The most frequently ($\geq 1/100$ to $< 1/10$) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment.

Blood and the lymphatic system disorders:

Uncommon: Anaemia

Rare: Agranulocytosis, leukopaenia, thrombocytopaenia, neutropaenia

Immune system disorders:

Rare: Anaphylaxis

Metabolism and nutrition disorders:

Uncommon: Decreased appetite

Rare: Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia

Psychiatric disorders:

Uncommon: Somnolence, insomnia

Nervous system disorders:

Common: Headache

Uncommon: Seizures, paraesthesia, dizziness, taste perversion

Rare: Tremor

Ear and labyrinth disorders:

Uncommon: Vertigo

Cardiac disorders:

Rare: Torsade de pointes, QT prolongation

Gastrointestinal disorders:

Common: Abdominal pain, vomiting, diarrhoea, nausea

Uncommon: Constipation, dyspepsia, flatulence, dry mouth

Hepatobiliary disorders:

Common: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased

Uncommon: Cholestasis, jaundice, bilirubin increased

Rare: Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage

Skin and subcutaneous tissue disorders:

Common: Rash

Uncommon: Drug eruption*, urticaria, pruritus, increased sweating

Rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculo-skeletal and connective tissue disorders:

Uncommon: Myalgia

General disorders and administration site conditions:

Uncommon: Fatigue, malaise, asthenia, fever



* Including Fixed Drug Eruption.

Paediatric population: The pattern and incidence of adverse reactions and laboratory abnormalities recorded, excluding the genital candidiasis indication, are comparable to those seen in adults.

4.9. OVERDOSE:

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antimycotics for systemic use, Triazole and tetrazole derivatives.

ATC code: J02AC01.

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

5.2. PHARMACOKINETICS PROPERTIES:

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

Absorption: After oral administration fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post dose. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.

Distribution: The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%). Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and



sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels. High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73µg/g and 7 days after cessation of treatment the concentration was still 5.8µg/g. At the 150mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4µg/g and 7 days after the second dose was still 7.1µg/g. Concentration of fluconazole in nails after 4 months of 150mg once-a-week dosing was 4.05µg/g in healthy and 1.8µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Metabolism: Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a moderate inhibitor of the isozymes CYP2C9 and CYP3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19.

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

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

5.3. PRECLINICAL SAFETY DATA:

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

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

Mutagenesis: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *Salmonella 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 1000µg/ml) showed no evidence of chromosomal mutations.

Reproductive toxicity: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20mg/kg or with parenteral doses of 5, 25, or 75mg/kg. There were no foetal effects at 5 or 10mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays



in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg to 320mg/kg embryoletality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification. The onset of parturition was slightly delayed at 20mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Lactose Monohydrate
- Magnesium Stearate
- Talcum Powder
- Hard Gelatin Capsule

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Keep out of reach of children.

Avoid exposure to heat light and humidity. Store between 15 to 30°C.

Improper storage may deteriorate the medicine.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/Alu blister packing, pack size is 1's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

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

6.7. DRUG PRODUCT SPECIFICATIONS:

BP Specs.



7. REGISTRATION / MARKETING AUTHORISATION HOLDER



Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
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044273

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16th October, 2006

10. DATE OF REVISION OF THE TEXT

فنگون کیسپول
(فلوکونازول)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

R.N-06/QC/08/2026_SmPC