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FLUCONAZOLE

FUNGICON™
 150 mg Capsule
 ANTI FUNGAL

PRODUCT NAME
 FUNGICON

DOSAGE FORM AND STRENGTH
 Capsules/150 mg

PHARMACOLOGIC CATEGORY
 Anti Fungal

PRODUCT DESCRIPTION
 White/Red coloured '2' size capsule with 'MICRO/MICRO' printed on capsule shells containing white granular powder.

FORMULATION/COMPOSITION

 Each capsule contains:
 Fluconazole USP..... 150 mg

PHARMACODYNAMICS AND PHARMACOKINETICS
Pharmacodynamics:

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mechanism of action

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

Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Susceptibility in vitro

In vitro, fluconazole displays antifungal activity against clinically common *Candida* species (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*), *C. krusei* is intrinsically resistant to fluconazole. The wild-type population of *C. glabrata* is of intermediate susceptibility (I) to fluconazole. The MICs and epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans*. The recently emerging species *C. auris* tends to be relatively resistant to fluconazole.

Fluconazole also exhibits activity in vitro against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

Pharmacokinetic/pharmacodynamics relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly, cure is less likely for infections caused by strains with a higher fluconazole MIC.

Pharmacokinetics:

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 concentrations 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 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g. Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolized 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 (see section 4.5). Fluconazole is also a strong inhibitor of the isozymes 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.

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR< 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by hemodialysis and to a lesser extent by peritoneal dialysis. After three hours of hemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics during lactation

A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of Fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 mg/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children

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

After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram·h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

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 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·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. Coadministration of diuretics did not significantly alter AUC or C_{max} . In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 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 characteristics of this group.

INDICATION(s)

Fluconazole is indicated in the following fungal infections

Fluconazole 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.

Fluconazole 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 Hematopoietic Stem Cell Transplantation).

Fluconazole is indicated in term newborn infants, infants, toddlers, children and adolescents aged from 0 to 17 years old:

Fluconazole is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Fluconazole 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.

DOSAGE AND MODE/ROUTE 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: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg once daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence. 200 mg once daily	Indefinitely at a daily dose of 200 mg

Coccidioidomycosis		200 mg to 400 mg once daily	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningial disease
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg once daily	In general, the recommended duration of therapy for candidia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidia.
Treatment of mucosal candidiasis	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg 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: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg 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	200 mg to 400 mg once daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
	- Chronic mucocutaneous candidiasis	50 mg to 100 mg 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	100 mg to 200 mg once daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
	- Oesophageal candidiasis	100 mg to 200 mg once daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
Genital candidiasis	- Acute vaginal candidiasis - Candidal balanitis	150 mg	Single dose
	- Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year).	150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150 mg once weekly maintenance dose	Maintenance dose: 6 months.
Dermatomycosis	- <i>tinea pedis</i> , - <i>tinea corporis</i> , - <i>tinea cruris</i> , - <i>candida</i> infections	150 mg once weekly or 50 mg once daily	2 to 4 weeks, <i>tinea pedis</i> may require treatment for up to 6 weeks
	- <i>tinea versicolor</i>	300 mg to 400 mg once weekly	1 to 3 weeks
		50 mg once daily	2 to 4 weeks
Prophylaxis of candidal infections in patients with prolonged neutropenia		150 mg 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.
		200 mg to 400 mg once daily	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm ³ .

Special populations
Elderly

Dosage should be adjusted based on the renal function (see "Renal impairment").

Renal impairment

Fluconazole is predominantly excreted in the urine as unchanged active substance. No adjustments in single dose therapy are necessary. In patients (including pediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg 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 hemodialysis)	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.

Hep

Size: 280 (L) x 420 (H) mm

Folding size: 65 x 100 mm

Carton size: 180 x 34 x 73 mm (Lock Bottom)

Bible Paper 40 gsm

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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 hypokalemia 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.

Coadministration of other medicinal products known to prolong the QT interval and which are metabolized 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 multiform develop.

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 metabolized through CYP2C9, CYP2C19 and CYP3A4, should be monitored.

Terfenadine

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

Excipients

Capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

PREGNANCY AND LACTATION (If applicable)

Pregnancy

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400 - 800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity.

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.

Lactation

Fluconazole passes into breast milk to reach concentrations similar to those in plasma. Breast-feeding may be maintained after a single dose of 150 mg 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.

Fertility

Fluconazole did not affect the fertility of male or female rats

INTERACTION(s)

Concomitant use of the following other medicinal products are contraindicated:

Cisapride: There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated.

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

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

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated.

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 *torsades de pointes*. Coadministration 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. Coadministration 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 (800 mg).

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 coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Hydrochlorothiazide: In a pharmacokinetic interaction study, coadministration 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: 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/documentary interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 coadministered with fluconazole. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.

Afentanil: During concomitant treatment with fluconazole (400 mg) and intravenous afentanil (20 µg/kg) in healthy volunteers the afentanil AUC_{0-∞} increased 2-fold, probably through inhibition of CYP3A4. Dose adjustment of afentanil 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

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

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. 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 indandione 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 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg 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 dose, 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 metabolised by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

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

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, it was shown in healthy volunteers that 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 when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored.

HMG-CoA reductase inhibitors: HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

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 280 mg once daily (two capsules) for the duration of the inhibitor use and provide close clinical monitoring.

Ivacafator: Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxyethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A4 inhibitors, such as fluconazole and erythromycin.

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 200 mg twice daily.

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

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/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.

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 were 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 (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, ibuprofen, 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 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC24 by 75% and C_{max} 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, and tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.

Theophylline: In a placebo-controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of 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.

MICRO LABS LIMITED, BANGALORE, INDIA						
1	Product Name	Fungicon			Colours Used ■ BLACK	
2	Strength	150 mg				
3	Component	Leaflet				
4	Category	Export - Philippines				
5	Dimension	280 (L) x 420 (H) mm				
6	Artwork Code	EXG-ML01I-1034/B				
7	Pharma Code	N/A				
8	Reason for Change	Size and New Regulation text				
		Prepared by (DTP)	Checked by (PD)	Approved by		
Sign	Kanthalraju L. <th>Head CQA</th> <th>Head Production/Packing (Site)</th> <th>Head QC (Site)</th> <th>Head QA (Site)</th>			Head CQA	Head Production/Packing (Site)	Head QC (Site)
Date	13-01-2022					