1. Name of the Medicinal Product:

1.1 Product Name

Generic Name or International Non-Proprietary Name (INN)

Fluconazole capsules BP 150 mg

Brand Name: - NA

1.2 Dosage Strength

Each hard gelatin capsule contains:
Fluconazole BP……..150 mg
Excipients…… Q.S.
Approved colour used in empty capsule shells.

1.3 Dosage Form

Hard Gelatin Capsules

2. Quality and Quantitative Composition:

2.1 Qualitative Declaration

Composition:

Each hard gelatin capsule contains:
Fluconazole BP……..150 mg
Excipients…… Q.S.
Approved colour used in empty capsule shells.

2.2 . Quantitative Declaration

White colour powder filled in size '2' empty hard gelatin capsules having blue colour cap and white colour body.

UNIT FORMULA:

STD Batch Size: 159.000 kg / 6.00 Lac Capsules Reference. MFR No: MFR/C-E250, Version No: 00

Sr. No	Ingredients	A.R No.	Specification	Overages	Quantity / in mg	Standard Qty in kg
Dry Mixing						
1.	Fluconazole	RM220011	BP	Nil	150.000	90.000
2.	Maize Starch	RM220443	BP	Nil	68.000	40.800
3.	Lactose	RM220003	BP	Nil	30.000	18.000
4.	Sodium Benzoate	RM204651	BP	Nil	2.000	1.200
5.	Talc	RM220005	BP	Nil	10.000	6.000
6.	Magnesium Stearate	RM22033	BP	Nil	3.000	1.800
7.	Colloidal Silicon Dioxide	RM220081	BP	Nil	2.000	1.200
8.	Empty Hard Gelatin Capsules Dark Blue/white Size "2"	RM220441	IH	2.0%	1.00 capsule	6,12,000 capsule
Average wt. of Capsules (265.000 mg ± 7.5 %)						

Note:

Active Material is calculated on assay or Potency basis.

BP = British Pharmacopoeia

- Theoretical net content per capsule = 265.00 mg.
- Empty capsule weight = 63.00 mg
- Average weight of filled capsule = 265 mg + 63.00 mg = 328.00 mg

- Justification for addition of Preservative
- Justification for addition of Preservative such as Sodium Benzoate in the preparation of Binder Salutation.
- All the raw material are analyst as per Pharmacopeial Specification for chemical & Microbial Limit test
- Purified Water used for the manufacturing is under monitoring program for Microbial Limit test
- Manufacturing area monitored as per the predefined frequency for environmental monitoring.

❖ As a an additional Methyl Sodium Benzoate added in the preparation binder solution to take care of Microbial Purity

3. Pharmaceutical Form:

White colour powder filled in size '2' empty hard Gelatin capsules having blue colour$_{cap}$ and white colour body

4. Clinical Particulars:

4.1 Therapeutic Indications:

Diflucan is indicated in the following fungal infections. Diflucan 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 unguinium (onychomycosis) when other agents are not considered appropriate.

Diflucan 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 HIVwho 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 (see section 5.1)).

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

Diflucan is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Diflucan can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4). Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, antiinfective 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: 400 mg on Day 1 Subsequent dose:	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	200200 mg once mg to 400 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 meningeal disease
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg 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

Treatment of mucosal	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent 100 mg to 200 mg once daily	candidemia 7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be
	- Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent 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
	- Candiduria	200 mg to 400 mg once daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune
	- Chronic atrophic	50 mg once daily	14 days
	- 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 compromisation and
Prevention of relapse of mucosal candidiasis in patients 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 or200 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	Maintenance dose: 6 months.

Dermatomycosis	- tinea pedis, - tinea corporis, - tinea cruris,	150 mg once weekly or 50 mg once daily	2 to 4 weeks, tinea pedis may require treatment for up to 6 weeks
	ndid i f ti - tinea versicolor	300 mg to 400 mg once	1 to 3 weeks
		50 mg once kl	2 to 4 weeks
	- tinea unguium (onychomycosis)	daily 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
Prophylaxis of candidal infections in patients with prolonged neutropenia		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

Special populations above 1000 ll 3

Elderly

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

Renal impairment

Diflucan 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 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 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 (see sections 4.4 and 4.8).

Paediatric population

A maximum dose of 400 mg 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. Diflucan is administered as a single daily dose.

For paediatric patients with impaired renal function, see dosing in " Renal impairment ".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: 6 mg/kg Subsequent dose: 3 mg/kg once daily	Initial dose may be used on the first day to achieve steady state levels more
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg once daily	rDepending on theapidly severity of the disease

- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 6 mg/kg once daily	Depending on the severity of the disease
- Prophylaxis of Candida in immunocompromised patients	Dose: 3 to 12 mg/kg once daily	Depending on the extent and duration of the induced neutropenia (see Ad lt logy)

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 fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Safety and efficacy for genital candidiasis indication in paediatric population has not been established. Current available safety data for other paediatric indications are described in section 4.8. 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 (see section 5.2).

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	A maximum dose of 12 mg/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 12 mg/kg every 48 hours should not be exceeded

Method of administration

Diflucan may be administered either orally (Capsules and Powder for Oral Suspension) or by intravenous infusion (Solution for Infusion), the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or vice versa, there is no need to change the daily dose.

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. Oral liquid formulations of fluconazole are available that are more suitable in this population.

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

4.3 Contraindications:

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients listed in section 6.1.

Coadministration of terfenadine is contraindicated in patients receiving Diflucan at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Coadministration 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 (see sections 4.4 and 4.5).

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, Diflucan 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.

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

Diflucan 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, see section 4.5

Hepatobiliary system

Diflucan should be administered with caution to patients with liver dysfunction. Diflucan 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 (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 very rare cases of QT prolongation and torsades de pointes in patients taking Diflucan. 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.

Diflucan 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 metabolised via the cytochrome P450 (CYP) 3A4.

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 StevensJohnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. 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.

Hypersensitivity

In rare cases anaphylaxis has been reported (see section 4.3).

Cytochrome P450

Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Diflucan 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 coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

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. Excipients

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

Diflucan capsules contain less than 1 mmol sodium (23 mg) per capsule, that is to say essentially „sodium-free".

4.5 Interaction with other medicinal products and other forms 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 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 (see section 4.3).

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 (see section 4.3). 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 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 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.

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:

During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 g/kg) in healthy volunteers the alfentanil AUC 10 increased 2-fold, probably through inhibition of CYP3A4.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

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, haematuria, 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 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 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 2.3fold, 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 Cmax 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 (dose- dependent) when fluconazole is coadministered 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 280 mg 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 200 mg 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 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.

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 Cmax and AUC of flurbiprofen was 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] 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, 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 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC24 by 75% and Cmin 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 Cmax of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavirs 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) 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.

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 5 mg once daily when it is combined with these drugs.

Tolvaptan:

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, 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:

Based on a case-report in one patient receiving combination therapy with all-transretinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour 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: (CYP2C9, CYP2C19 and CYP3A4 inhibitor):

Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in Cmax and AUCτ 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 Cmax 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:

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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

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 ≤ 450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radiohumeral 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 (see section 5.3).

Before becoming pregnant a washout period of approximately 1 week (corresponding to 5-6 half- lives) is recommended after a single-dose or discontinuation of a course of treatment (see section

5.2). 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 (see section 5.2). 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 Diflucan and any potential adverse effects on the breast-fed child from Diflucan or from the underlying maternal condition.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Diflucan on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Diflucan and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

Summary of safety profile

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section 4.4).

The most frequently (≥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.

The following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ	Common	Uncommon	Rare	Not Known

Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia	
Immune system disorders			Anaphylaxis	
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolae hypertriglyceridaemi hypokalaemia	
Psychiatric disorders		Somnolence, insomnia		
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor	
Ear and labyrinth disorders		Vertigo		
Cardiac disorders			Torsade de pointes (see section 4.4), QT prolongation.	
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation dyspepsia, flatulence, dry mouth		
Hepatobiliary disorders	Alanine aminotransferase increased aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)	Cholestasis , Jaundice, bilirubin	Hepatic failure, hepatocellular necrosis,hepatitis , hepatocellular damage	

Skin and subcutaneous tdii sorders	Rash (see section 4.4)	Drug eruption* (see section 4.ur4ti)caria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis, (see 4.4), i Stevens-Johnsyndrsoonme (see 4.4)ti, acute generalised exanthematous-pustulosis (see section 4.4), dermatitis exfoliative,	Drug reaction with iand hsiylistemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders		Myalgia	angioedema, face	
General disorders and		Fatigue, malaise, asthenia, fever		

* including Fixed Drug Eruption

Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

There have been reports of overdose with Diflucan. 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 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.

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. glabrata shows reduced susceptibility to fluconazole while C. krusei and C. auris are resistant to fluconazole. The MICs and epidemiological cut-off value (ECOFF) of fluconazole for C. guilliermondii are higher than for C. albicans. Fluconazole also exhibits activity in vitro against

Cryptococcus neoformans and Cryptococcus. gattii as well as the endemic moulds Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum and Paracoccidioides brasiliensis.

Pharmacokinetic/pharmacodynamic 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.

Mechanisms of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy in vivo and clinically.In usually susceptible species of Candida, the most commonly encountered mechanism of resistance development involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutation, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways.There have been reports of superinfection with Candida species other than C. albicans, which often have inherently reduced susceptibility (C. glabrata) or resistance to fluconazole (e.g. C. krusei, C. auris). Such infections may require alternative antifungal therapy. The resistance mechanisms have not been completely elucidated in some intrinsically resistant (C. krusei) or emerging (C. auris) species of Candida.

EUCAST Breakpoints

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility in vitro and clinical response EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing-Subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for Candida species (EUCAST Fluconazole rationale document (2020)-version 3; European Committee on Antimicrobial

Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs, Version 10.0, valid from 2020-02-04). These have been divided into non-species related breakpoints, which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S≤/R>) in mg/L						Non-species related breakpoints[A] S≤/R> in mg/L
	Candida albicans	Candida dubliniensi	Candida glabrata	Candid krusei	Candida parapsilosi	Candida tropicalis	
Fluconazole			0.001*/16				

S = Susceptible, R = Resistant

A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

* = The entire C. glabrata is in the I category. MICs against C. glabrata should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. I - Susceptible, increased exposure: A microorganism is categorised as Susceptible, increased exposure when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

5.2 Pharmacokinetic 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 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 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 (see section 4.5). 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.

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 haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis 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 Diflucan. 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 ml/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 paediatric patients from 5 studies; 2 singledose 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 µgh/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 wasapproximately880ml/kg aftermultiple doses.A higherfluconazole 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 50mgoraldose offluconazole. Tenofthesepatients were concomitantlyreceiving diuretics. The Cmax 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 Cmax. 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 reduce renal function characteristics of this group.

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 for24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/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. Cytogeneticstudies in vivo (murine bone marrow cells, following oral administration of fluconazole) and invitro (human lymphocytes exposed to fluconazole at 1000 μg/ml) showed no evidence ofchromosomal mutations.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5,10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg. There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality 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 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/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 (see section 5.1).

6 Pharmaceutical Particulars:

6.1 List of excipients:

- Maize Starch
- Lactose
- Sodium Benzoate
- Talc
- Magnesium Stearate
- Colloidal Silicon Dioxide
- Empty Hard gelatin Scarlet/ Scarlet Size “2”

6.2 Incompatibilities:

None stated

6.3 Shelf life:

3 Years from the date of manufacture.

6.4 Special precautions for storage:

Store below 30°C. Keep out of the reach of children

6.5. Nature and contents of outer packaging:

Pack 1 Capsule in a blister with the help of Printed Alu foil and Alu base foil in the arrangement of 1x10’s. Pack such 1 Blister in one printed inner carton in the arrangement of 1x10’s. Pack such 10 Printed inner cartons in a printed outer carton in the arrangement of 10x1x10’s.

6.6 Special Precautions for Disposal
Not applicable.

7 Applicant:

Carnauba Intergrated Health Care Ltd, Broad Street Lagos

Island, Lagos.

Manufacturer:

SURMOUNT LABORATORIES PVT. LTD.

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