SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 100 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100, mg fluconazole.

Excipient with known effect: Each tablet contains 97.5 mg of lactose (as lactose monohydrate)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatine capsule

Blue cap, white body with the imprint FC100, containing a white odourless powder,

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole is indicated in the following fungal infections (see section 5.1).

Fluconazole is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- 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.

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 (see section 5.1)).

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 (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, anti-infective therapy should be adjusted accordingly.
Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration

Posology
The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that active fungal infection has

subsided. An inadequate period of treatment may lead to recurrence of active infection.

Administration in 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 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 candidemia.
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 atrophic candidiasis	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 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	- *tinea pedis,* - *tinea corporis,* - *tinea cruris,* - *candida* infections	150 mg once weekly or 50 mg once daily	2 to 4 weeks, *tinea pedis* may require treatment for up to 6 weeks
	- *tinea versicolor*	300 mg to 400 mg once weekly	1 to 3 weeks
		50 mg once daily	2 to 4 weeks
	- *tinea unguium* (*onychomycosis*)	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.
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 above 1000 cells per mm^3.

Special populations

Administration in elderly patients
Dosage should be adjusted based on the renal function (see "*Renal impairment*").

Patients with Renal impairment
Fluconazole is predominantly excreted with urine in unchanged active substance. No adjustments in single dose therapy are required. 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)	**Percentage 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. Fluconazole 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 rapidly
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg once daily	Depending on the severity of the disease
- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 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 Adults posology)

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 every 72 hours	A maximum dose of 12 mg/kg every 72 hours should not be exceeded
Term newborn infants	The same mg/kg dose as for infants, toddlers and	A maximum dose of 12 mg/kg every 48 hours

(from 15 to 27 days)	children should be given every 48 hours	should not be exceeded

Mode of administration
Fluconazole 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 fluconazole, other azole derivatives or to any of the excipients listed in section 6.1.
Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Co-administration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine, and erythromycin are contraindicated in patients receiving fluconazole (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, fluconazole should not be used for tinea capitis.

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

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

Renal system
Fluconazole should be administered with caution in patients with renal dysfunction (see section 4.2).

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 'The effect of fluconazole on other medicinal products'.

Hepatobiliary system
Fluconazole should be administered with caution to patients with liver dysfunction.

Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, gender or age of the 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 QT-interval prolongation 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 torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant 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 in patients with potentially proarrythmic conditions.

Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Halofantrine
Halofantrine has been shown to prolong QTc at the recommended therapeutic

dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is not recommended (see section 4.5).

Dermatological reactions
Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson 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 with many medicinal products. If a rash develops in a patient treated for a superficial fungal infection, which is considered attributable to fluconazole, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole should be discontinued if bullous lesions or erythema multiforme develop.

Hypersensitivity
Anaphylactic reactions in rare cases have been reported (see section 4.3 and 4.8).

Cytochrome P450
Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).

Terfenadine
The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

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.

Fluconazole 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 interaction

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports about cardiac cases 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 QT interval. Concomitant treatment with fluconazole and cisapride is contra-indicated (see section 4.3).

Terfenadine: Due to the occurrence of serious cardiac dysrhythmias secondarily to prolongation of the QTc-interval in patients on treatment with azole antifungals products concomitantly with terfenadine, interaction studies have been performed. One study with 200 mg fluconazole daily did not show any prolongation of the QTc-interval. Another study with 400 mg and 800 mg fluconazole daily showed that fluconazole in doses of 400 mg or more daily significantly increases the plasma level of terfenadine, if the two medicinal products are taken concomitantly. Concomitant treatment with terfenadine and fluconazole doses of 400 mg or more is contra-indicated (see section 4.3). At fluconazole doses below 400 mg, the patient should be closely 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. Concomitant treatment with fluconazole and astemizole is contra-indicated due to the potential for serious, even fatal, cardiac effects. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and pimozide is contraindicated. (see section 4.3).

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 (see section 4.3).

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 (see section 4.3).

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

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an 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 (see section 4.4).

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 % reduction of AUC and 20 % shorter half-life of fluconazole. Increase of dosage should be considered in patients concomitantly receiving rifampicin.

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

Effect of fluconazole on the metabolism of other medicinal products:
Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 3A4. Fluconzole is also an inhibitor of the isozyme CYP2C19. Besides the observed/documented interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9, CYP2C19 and CYP3A4 co-administered with fluconazole. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme-inhibiting effect of fluconazole may persist for 4–5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

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: Concomitant intake of fluconazole 400 mg and alfentanil 20 µg/kg intravenously in healthy volunteers increased the alfentanil AUC10 by approximately 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 -amitnptyline 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 increase 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 warfarin metabolism via CYP2C9. The prothrombin time must be closely monitored in patients on treatment with coumarin derivatives or indanedione. Dose adjustment of the anticoagulant may be necessary.

Benzodiazepines (Short Acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increase 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 it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, a reduction of the benzodiazepine dose should be considered, and the patients should be closely monitored.

Calcium channel antagonists: Certain calcium channel antagonists (nifedipine, isradipine, nicardipine, amlodipine, verapamil and felodipine) are metabolised via CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

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

Celecoxib: During concomitant treatment with Fluconazole 200 mg daily and celecoxib 200 mg resulted in 68 % and 134 % increase in celecoxib Cmax and AUC, respectively. Halving the Celecoxib dose is recommended to patients

concurrently treated 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 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 that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). If concomitant therapy is necessary, patients should be observed symptoms of myopathy and rhabdomyolysis and creatine kinase (CK) should be monitored. HMG-CoA reductase inhibitors should be discontinued if CK levels show a marked increase, or if myopathy or 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):
Coadministration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethylivacaftor (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-3174), which is responsible for a large part of the angiotensin II receptor antagonism that occurs with losartan therapy. 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. Dosage adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs:
The Cmax and AUC of flurbiprofen were increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] 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 metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Repeated concomitant administration of 200 mg fluconazole and 250 mg phenytoin may increase the levels of phenytoin AUC by 75 % and Cmin by 128 %. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: A liver transplant recipient receiving prednisone developed acute

adrenal cortex insufficiency when a three-month course of fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity, leading to an increase in the metabolism of prednisone. Patients receiving long-term therapy with fluconazole and prednisone should be closely monitored for signs of adrenal cortex insufficiency when fluconazole is withdrawn discontinued.

Rifabutine: Fluconazole concomitantly with rifabutine have appeared, leading to increased serum levels of rifabutine and increase in the AUC of rifabutin up to 80%. Uveitis in patients treated concomitantly with fluconazole and rifabutine has been reported. Patients who receive rifabutine and fluconazole concomitantly must be closely followed and symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC of saquinavir with approximately 50%, Cmax with approximately 55% and decreases clearance of saquinavir with approximately 50% 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. Dosage adjustment of saquinavir may be necessary.

Sulphonyl urea: Fluconazole has been shown to prolong the serum half-life of concomitantly administered sulphonyl urea (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during co-administration.

Theophylline: In a placebo controlled interaction study, intake of fluconazole 200 mg for 14 days resulted in 18 % decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed for signs of theophylline toxicity during fluconazole therapy, and the theophylline dose should be adjusted as necessary 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-trans-retinoid 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 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 C_{max} and AUC_{τ} 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 side-effects. Dosage 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

Women of childbearing potential
Before initiating treatment, the patient should be informed of the potential risk to the fetus.

After single dose treatment, a washout period of 1 week (corresponding to 5-6 half-lives) is recommended before becoming pregnant (see section 5.2).

For longer courses of treatment, contraception may be considered, as appropriate, in women of childbearing potential throughout the treatment period and for 1 week after the final dose.

Pregnancy

Observational studies suggest an increased risk of spontaneous abortion in women treated with fluconazole during the first **and/or second** trimester **compared to women not treated with fluconazole or treated with topical azoles during the same period.**

Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤ 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.

Available epidemiological studies on cardiac malformations with use of fluconazole during pregnancy provide inconsistent results. However, a meta-analysis of 5 observational studies including several thousand pregnant women exposed to fluconazole during the first trimester finds a 1.8-2 fold increased risk of cardiac malformations when compared to no fluconazole use and/or topical azoles use.

Case reports describe a pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during pregnancy for 3 months or more, in the treatment of coccidioidomycosis. The birth defects seen in these infants include brachycephaly, ears dysplasia, giant anterior fontanelles, femoral bowing and radio-humeral synostosis. A causal relationship between fluconazole use and these birth defects is uncertain.

Fluconazole in standard doses and short-term treatment should not be used during pregnancy unless clearly necessary.

Fluconazole in high doses or in prolonged regimens should not be used during pregnancy except for life threatening infections.

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma (see section 5.2). Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breastfeeding 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 (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Fluconazole on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Fluconazole 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 undesirable effects have been observed and reported during treatment with fluconazole with the following frequencies: Very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1000, <1/100), rare (> 1/10000, <1/1000) and very rare (>1/10000), not known (cannot be estimated from the available data).

System Organ Class	**Common**	**Uncommon**	**Rare**	**Not Known**
Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia	
Immune system disorders			Anaphylaxis	
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia	

Psychiatric disorders		Somnolence, insomnia		
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor	
Ear and labyrinth disorders		Vertigo		
Cardiac disorders			Torsade de pointes (see section 4.4), QT prolongation (see section 4.4)	
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation dyspepsia, flatulence, dry mouth		
Hepato-biliary disorders	Alanine Aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)	Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)	
Skin and subcutaneous tissue disorders	Rash (see section 4.4)	Drug eruption* (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis, (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous -pustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, connective tissue bone disorders		Myalgia		
General disorders and administration		Fatigue, malaise,		

site conditions		asthenia, fever		

* including Fixed Drug Eruption.

Paediatric Population

The pattern and incidence of side effects and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults, 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 the yellow card scheme at www.mhra.gov.uk/yellowcard or search for MHRA yellow card in the google play or apple app store.

4.9 Overdose

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

In case of overdosing the treatment is symptomatic with supporting measures and gastric lavage, if necessary. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably increase the elimination rate. Haemodialysis for 3 hours decreases the plasma levels with approx. 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 shown to effect testosterone plasma concentrations in males or the 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.

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 breakpoint [A] S</R> in mg/L
	Candida albicans	Candida dubliniensis	Candida glabrata	Candida krusei	Candida parapsilosis	Candida tropicalis	
Fluconazole	2/4	2/4	0.001*/16	--	2/4	2/4	2/4

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:

Fluconazole is well absorbed after oral intake. The absolute bioavailability is above 90 %. The oral absorption is not affected by concomitant food intake. The maximum fasting plasma concentration is reached 0.5–1.5 hours after dose intake. Plasma concentrations are proportional to dose. 90 % of the steady-state level is reached 4–5 days after dosing once daily.

Intake of a double dose on day 1 results in plasma concentrations of approx. 90 % of steady-state on day 2.

Distribution:

The volume of distribution corresponds to the total body water. The protein binding in plasma 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 the concentration of fluconazole in the cerebrospinal fluid is approximately 80 % of the corresponding plasma concentration.

In stratum corneum, epidermis-dermis and in exocrine sweat higher concentrations of fluconazole are reached compared to those in serum. Fluconazole is accumulated in 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 a dose of 150 mg once weekly the concentration of fluconazole in stratum corneum on day 7 was23.4 mg/g and 7 days after the second dosing it was still 7.1 mg/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:

The half-life in plasma is approximately 30 hours. The major route of excretion is renal, with approximately 80 % of the taken dose is excreted in the urine in non-metabolized form. Fluconazole clearance is proportional to the 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 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 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 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.

5.3 Preclinical safety data

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

Carcinogenesis Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10 mg/kg/day. 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 S. typhimurium and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000μg/ml) showed no evidence of chromosomal mutations.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 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 50nmg/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

Lactose monohydrate,
Maize starch,
Magnesium stearate,
Sodium lauryl sulfate,
Colloidal silicon dioxide,

Capsule shell contains:
Titanium dioxide (E171),
Indigo Caramine (E 132),
Gelatin

Printing ink composition:
Shellac,
Isopropyl alcohol,
Black iron oxide (E 172),
N-Butyl alcohol,
Propylene glycol (E 1520),
Ammonium hydroxide (E 527)

6.2 Incompatibilities

No incompatibilities are known to date.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

The hard capsules are packed in PVC white, opaque/aluminium blisters and inserted into a carton.

Pack sizes*:* 1, 7, 10, 14, 20, 30, 50 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
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RG21 8SR
United Kingdom

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