1. NAME OF THE MEDICINAL PRODUCT
Flucosten Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of reconstituted suspension contains 10 mg fluconazole.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM
Powder for oral suspension

White to off-white powder for oral suspension providing a white to off-white suspension after reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Flucosten is indicated in the following fungal infections (see section 5.1).

Flucosten 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

Flucosten 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)).

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

Flucosten is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis and 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, 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

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Adults

Indications		Posology	Duration of treatment
Cryptococcosis	- Treatment of cryptococcal meningitis	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg once daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.	200 mg once daily	Indefinitely at a daily dose of 200 mg
Coccidioidomycosis		200 mg to 400 mg once daily	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for 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

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

Renal impairment
Flucosten 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. Flucosten 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 (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
Flucosten is administered orally (Capsules and Powder for Oral Suspension).

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.

Flucosten can be taken with or without food.

For instructions on reconstitution of the medicinal product before administration, see section 6.6. The

reconstituted suspension will provide a white to off-white suspension after reconstitution.

For dose conversion of the powder for oral suspension from mg/ml to ml/kg body weight (BW) for paediatric patients, see section 6.6.

For adult patients, please calculate the dose in ml to administer according to the posology in mg recommended and the product strength.

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

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in haematological, hepatic, renal and other biochemical function test results have been observed during treatment with fluconazole but the clinical significance and relationship to treatment is uncertain.

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

There is some evidence that in some patients with cryptococcal meningitis, the mycological response during fluconazole treatment may be slower compared with treatment with amphotericin B in combination with flucytosine. This should be taken into account for the treatment choice of patients with severe cryptococcal meningitis.

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 to 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 is described in section 4.5

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.

Patients who died with severe underlying diseases and who have received multiple dose of fluconazole had post-mortem findings which included hepatic necrosis. These patients were receiving multiple concomitant medications, some known to be potentially hepatotoxic and/or had underlying diseases that could have caused hepatic necrosis.

In cases of fluconazole-associated hepatotoxicity, no obvious relationship to the total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of fluconazole therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be closely monitored for 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). Fluconazole should be immediately discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with fluconazole and the patient should consult a physician.

Cardiovascular System
In rare cases, as with other azoles, anaphylaxis has been reported.
Some azoles, including fluconazole, have been associated with the prolongation of the QT interval on the electrocardiogram. 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. Although the association of fluconazole and QT prolongation has not been fully established, fluconazole should be used with caution in the following patients with potentially proarrythmic conditions such as:
• Congenital or documented acquired QT prolongation
• Cardiomyopathy in particular where heart failure is present
• Sinus bradycardia
• Existing symptomatic arrhythmias
• Electrolye disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia.
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 interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore 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. 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 potent CYP2C9 and CYP2C19 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole treated patients who are concomitantly treated with medicinal products 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).

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 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: As fluconazole inhibits cytochrome p450 isoenzyme 3A4, concomitant administration of fluconazole with astemizole may increase the serum levels / decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation, potentially fatal arrhythmias (including rare occurrences of torsades de pointes). 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 torsades 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).
Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be made when both drugs are combined, notably with high dose fluconazole (800mg).

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 (see section 4.4).

Concomitant use of the following other medicinal products lead to precautions and dose adjustments:
The effect of other medicinal products on fluconazole
Rifampicin (Rifampin): 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, 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[1], although the prescriber will have to take this into account.
[1] Mesure R. Protocol 245. An open placebo-controlled crossover study to determine any effect of concomitant diuretic treatment on fluconazole pharmacokinetics in healthy volunteers.

The effect of fluconazole on other medicinal products
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 2C19, and a moderate inhibitor of CYP3A4. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 (inc. HIV protease inhibitors such as ritonavir and indinavir) 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 (see section 4.3).
Alfentanil: In a placebo-controlled and crossover interaction study on healthy volunteers, the administration of doses of 400 mg of oral or intravenous fluconazole prior to the intravenous administration of alfentanil 20

g/kg caused a 55% reduction in alfentanil clearance by inhibiting its metabolism (probably through inhibition of CYP3A4), thus its effects may be extended. If concurrent treatment with alfentanil is necessary in patients who are being treated with fluconazole, decreasing the dose of alfentanil should be considered, and the patients must be appropriately monitored.
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 A. fumigatus. The clinical significance of results obtained in these studies is unknown.
Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2 fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or 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, lorazepam, oxazepam, temazepam, Lormetazepam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam seems greater following oral administration of fluconazole than with intravenous administration. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7 fold and 2.2 fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4 fold and 2.3 fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients must be appropriately monitored.
Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect.
Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.
Celecoxib: During concomitant treatment with fluconazole (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 when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.
Immunosuppresors (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. However, in another multiple dose study using 100mg daily of fluconazole, ciclosporin levels were not affected in bone marrow transplant patients. Therefore monitoring the plasma concentration of ciclosporin is recommended in patients receiving fluconazole and dose reduction of

ciclosporin may be required depending on ciclosporin concentration.
Everolimus: Although not studied in vivo or in vitro, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.
Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.
Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.
Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E 31 74) which is responsible for most of the angiotensin II receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.
Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.
Non-steroidal anti-inflammatory drugs (NSAIDs): 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 metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.
Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin and the conconcomitant administration of fluconazole and phenytoin may increase phenytoin levels to a clinically significant degree. 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%. If it is necessary to administer both drugs concomitantly, serum phenytoin concentration levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels and avoid phenytoin toxicity.
Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.
Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.
Saquinavir: Fluconazole increases the AUC and C max of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.
Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Fluconazole and sulphonylureas may be concurrently administered to diabetic patients, but the possibility of a hypoglycaemic episode must be considered therefore frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended.
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.
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, 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: Two pharmacokinetic studies have exhibited increases in zidovudine levels, probably caused by the decrease in zidovudine conversion into its main metabolite. One study determined zidovudine levels in patients with AIDS or ARC before and after the administration of 200 mg of fluconazole daily for 15 days. A significant increase of the AUC for zidovudine was observed (20%). A second randomised, two periods, crossover, two treatment study studied the zidovudine levels in patients infected with HIV. In two occasions, with an interval of 21 days, the patients received 200 mg of zidovudine every 8 hours with or without 400 mg of fluconazole daily for 7 days. The Cmax and AUC of zidovudine increased significantly (84% and 74% respectively) during the combined administration with fluconazole, 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. Those patients receiving this association must be monitored regarding the occurrence of zidovudine-related undesirable effects. 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 area under the curve (AUC)s 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.
Ivacaftor: 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 dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.
Although no interaction studies have been performed with other drugs, the possible occurrence of other similar pharmacological interactions is not rejected.

4.6 Pregnancy and Lactation

Pregnancy

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.
There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole and these incidents is unclear.
Studies in animals have shown reproductive toxicity (see section 5.3).
Fluconazole at standard doses and short-term treatment should not be used in pregnancy unless clearly necessary. Fluconazole in high doses 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 lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

4.7 Effects on ability to drive and use machines

Experience with fluconazole indicates that treatment with this drug is unlikely to affect the patient's ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions associated with fluconazole observed in clinical trials and post-marketing studies are listed below:

Frequencies are defined as:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1000 to <1/100)

Rare (≥1/10,000 to <1/1000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Within each frequency group, undesirable effects are presented in order of decreasing seriousness. Adverse events with very common frequency (≥1/10) until now have not been recognised.

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1000)**	**Very rare (<1/10,000)**	**Not known**
Infections and infestations					infection due to resistance microorganisms
Blood and lymphatic system disorders		anaemia	agranulocytosis, leucopenia, neutropenia, thrombocytopenia		
Immune system disorders			anaphylaxis	angiodemia, face oedema	
Metabolism and nutrition disorders		decreased appetite	hypercholesterolemia, hypertriglyceridemia, hypokalaemia		
Psychiatric disorders		insomnia, somnolence			
Nervous system disorders	headache	seizures, convulsions, dizziness, paraesthesia, taste perversion, tremor, vertigo			
Cardiac disorders			ventricular arrhythmia (QT prolongation, torsades de pointes) - see section 4.4		
Gastrointestinal disorders	vomiting, nausea, abdominal pain, diarrhoea	dyspepsia, flatulence, anorexia, constipation, dry mouth			
Hepatobiliary disorders	increase in the serum activities of liver-derived enzymes such as blood alkaline phosphatase (ALP), alanine aminotransferase (ALT) and	cholestasis, bilirubin increased, jaundice, hepatotoxicity	hepatitis, hepatocellular necrosis, hepatic failure with isolated fatalities. The appropriate laboratory values should be very closely monitored (see section 4.4)		

	aspartate aminotransferase (AST)				
Skin and subcutaneous tissue disorders	maculopapular erythema, rash	urticaria, pruritus, increased sweating, drug eruption*	exfoliative skin disorders (Stevens-Johnson syndrome), acute generalised exanthematous pustulosis, dermatitis exfoliative, angioderma, face oedema, alopecia	exfoliative skin disorders (toxic epidermal necrolysis or Lyell syndrome)	
Musculoskeletal and connective tissue disorders		myalgia			
Renal and urinary disorders		changes in renal function tests			
General disorders and administration site conditions		fatigue, malaise, asthenia, fever			
* = including fixed drug eruptions					

Paediatric population
The pattern and incidence of side-effects and laboratory abnormalities recorded during paediatric use are comparable to those seen in adults.

4.9 Overdose
Cases of overdose with fluconazole have been reported and one case of a 42-year old patient infected with the human immunodeficiency virus who exhibited hallucinations and paranoid behaviour after reporting that he had taken 8,200 mg of fluconazole. The patient was hospitalised and the symptoms resolved in 48 hours.
Symptomatic treatment may be suitable in the event of an overdose, with maintenance of vital signs and gastric lavage if necessary.
Fluconazole is eliminated mainly through urine; therefore, forced diuresis will very probably increase the elimination rate. A three-hour haemodialysis session reduces plasma levels to approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antimycotic (triazole derivatives)
ATC code: J02 AC 01
General properties
Fluconazole is a bis-triazole antifungal drug that belongs to the new class of triazole antifungal drugs.
Mode of action
Fluconazole is a powerful and specific inhibitor of the fungal synthesis of sterols. It acts by inhibiting cytochrome P450 14∝demethylase in susceptible fungi which converts lanosterol into ergosterol, an essential lipid component of the fungal membrane.
Fluconazole is highly specific for cytochrome P-450-dependent fungal enzymes. A daily dose of 50 mg of fluconazole, administered for a maximum period of up to 28 days, has demonstrated not to affect plasma concentrations of testosterone in males or steroid concentrations in women of child-bearing age.
A daily dose of 200-400 mg of fluconazole does not have a clinically significant effect upon the levels of endogenous steroids or on their response to ACTH stimulation in healthy volunteers. Interaction studies with antipyrine indicate that fluconazole, at single or multiple doses of 50 mg, does not affect its metabolism.
Most fungi show *in vivo* a clear sensitivity to fluconazole greater than the sensitivity they show *in vitro*. This

is a common problem to all azole antifungal drugs
Fluconazole, both orally and intravenously, has demonstrated to be active in a wide variety of animal fungal infection models. Said activity has been demonstrated in opportunist mycoses, such as infections by *Candida* spp., including systemic candidiasis in immunocompromised animals; infections by *Cryptococcus neoformans* , including intracranial infections; infections by *Microsporum*spp., and infections by *Trichophyton* spp.
Fluconazole has demonstrated to be active in endemic mycosis animal models, including infections by *Blastomyces dermatitidis*; infections by *Coccidioides immitis*, including intracranial infection; and infections by *Histoplasma capsulatum* in normal and immunocompromised animals.

Mechanism of resistance
Occasional isolates of fluconazole-resistant *Candida albicans* have been reported in patients receiving prolonged AIDS treatments. As with amphotericin B and any other antiinfectious drug, isolates that are resistant to a specific treatment may occur especially in immunocompromised patients receiving treatment with that drug.

Breakpoints

	Species related breakpoints					**Non-species related breakpoint***
	Candida albicans	Candida glabrata	Candida krusei	Candida parapsilosis	Candida tropicalis	
Fluconazole	2/4	IE	-	2/4	2/4	2/4

* 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 with organisms that do not have specific breakpoints
- Susceptibility testing not recommended as specires is a poor target for therapy with the drug.
IE – there is insufficient evidence that the species in question is a good target for therapy with the drug

Susceptibility
The prelevance of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable

Commonly susceptible species
C albicans
C kefyr
C lusitaniae
C parapsilosis
Species for which acquired resistance may be a problem
C dublinien
C famata
C guillermondii
C,pelliculosa
C tropicalis
Inherently resistant organisms
C glabrata
C krusei

The efficacy of fluconazole in tinea capitis has been studied in 2 randomised controlled trials in a total of 878 patients, comparing fluconazole with griseofulvin. Fluconazole at 6mg/kg/day for 6 weeks was not superior to griseofulvin administered at 11mg/kg/day for 6 weeks. The overall success rate at 6 weeks was

low (fluconazole 6 weeks: 18.3%; fluconazole 3 weeks: 14.7%; griseofulvin: 17.7%) across all the treatment groups. These findings are not inconsistent with the natural history of tinea capitis without therapy.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetic properties of fluconazole are similar following its oral or intravenous administration. Fluconazole is well absorbed orally, with plasma levels (and systemic bioavailability) of more than 90% with respect to the levels reached following intravenous administration. Oral absorption is not affected by the combined administration of food. Peak plasma concentrations are obtained between 0.5 and 1.5 hours post-dose, with an elimination half-life of approximately 30 hours.

Distribution

Plasma concentrations are proportional to the doses. 90% of the equilibrium state levels are reached 4 or 5 days following multiple doses once daily. The administration of a higher dose on the first day, double the usual daily dose, increases plasma levels to 90% of the equilibrium state levels on the second day. The apparent distribution volume is close to the total body water. Binding to plasma proteins is low (11-12%). Fluconazole penetration in all the body fluids studied is high. Fluconazole levels in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, the fluconazole concentration in cerebrospinal fluid is approximately 80% of the plasma concentration.

High concentrations of fluconazole are reached in the stratum corneum, dermis and epidermis and in eccrine sweat, higher than serum concentrations. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the fluconazole concentration after twelve days was 73 g/g, and seven days after discontinuation of the treatment, it was still 5.8 g/g. At a dose of 150 mg once a week, the fluconazole concentration in the stratum corneum on day seven was 23.4 g/g and seven days after the second dose it was still 7.1 µg/g.

The concentration of fluconazole in the nails after four months of administration of 150 mg once a week, was 4.05 g/g in healthy nails and 1.8 µg/g in affected nails. Fluconazole could still be measured in nail samples taken six months after treatment completion.

Metabolism-Elimination

Its elimination is preferably renal, 80% of the dose appearing in urine without modification. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

Its long elimination half-life allows administration of a single dose in the treatment of genital candidiasis and of a daily dose or a weekly dose in the treatment of any other mycoses it is indicated for.

One study compared the plasma and saliva concentrations after a single dose of 100 mg of fluconazole administered in oral suspension (by rinsing and keeping in the mouth for two minutes and swallowing) or in a capsule. The maximum concentration of fluconazole in saliva with the suspension was observed five minutes after swallowing, and was 182 times greater than the maximum concentration in saliva after capsule administration, reached four hours after swallowing. After approximately four hours, fluconazole concentrations in saliva were similar. The mean AUC (0-96) in saliva was significantly higher following administration of the suspension compared to the capsule. There were no significant differences in the elimination rate from saliva or in the pharmacokinetic parameters for both formulations.

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 1 study were not interpretable due to changes in formulation partway through the study. Additional data were available from a compassionate use study.

After administration of 2 – 8mg/kg fluconazole to children between ages of 9 months to 15 years, a 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 880ml/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 950ml/kg.

5.3 Preclinical safety data

Preclinical data for conventional studies on repeat-dose/general toxicity, genotoxicity or carcinogenicity indicate no special hazard for humans not already considered in other sections of the SPC.
In reproduction toxicity studies in rats, an increased incidence of hydronephrosis and extension of renal pelvis was reported and embryonal lethality was increased. An increase in anatomical variations and delayed ossification was noted as prolonged delivery and dystocia. In reproduction toxicity studies in rabbits, abortions were recorded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sucrose
Sodium citrate
Citric acid
Sodium benzoate
Xanthan gum

6.2 Incompatibilities
None known.

6.3 Shelf life
Unopened bottle: 4 years.
Reconstituted suspension: The reconstituted oral suspension has a shelf life of 14 days after reconstitution.

6.4 Special precautions for storage
Store belowe 30°C.

6.5 Nature and contents of container
Amber PET bottle with 28mm Aluminium screw cap. A measuring cup is included to measure 5 and 10ml.
Pack sizes of 1 bottle containing 35ml.

6.6 Special precautions for disposal and other handling
INSTRUCTIONS FOR RECONSTITUTION
Turn the bottle upside down and tap it gently until all the powder moves freely. Add 25ml of boiled and cooled water and shake vigorously. Shake again before use. A whitish suspension is obtained after its reconstitution with water. Dilution is not appropriate. The reconstituted suspension should be stored in the refrigerator and used within 2 weeks of preparation.
Any unused product should be disposed of in accordance with local requirements.

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