Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FLUCONAZOLE 2 mg/mL FRESENIUS Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL solution for infusion contains 2 mg fluconazole.

Each 50 mL of solution for infusion contains 100 mg fluconazole.

Each 100 mL of solution for infusion contains 200 mg fluconazole.

Each 200 mL of solution for infusion contains 400 mg fluconazole.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear to almost colourless sterile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Once the results of cultures and other laboratory studies become available, anti-infective therapy should be adjusted accordingly.

FLUCONAZOLE FRESENIUS is indicated for the treatment of the following conditions in adults and children:

1. Cryptococcal meningitis and maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS

2. Systemic candidiasis
3. Oropharyngeal and oesophageal candidiasis
4. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy and radiotherapy.

4.2 Posology and method of administration

Posology

Treatment with FLUCONAZOLE FRESENIUS should be initiated by a medical practitioner experienced in the management of invasive fungal infections.

The dose is dependent on the type and the severity of the infection.

The treatment of infections requiring multiple dosing must be continued until clinical parameters or laboratory results show that the active fungal infection has subsided. An insufficient treatment period may lead to recurrence of the active infection.

Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

Fluconazole is also available for oral treatment. The patient should be switched from intravenous to oral administration as soon as possible. It is not necessary to change the daily dose of fluconazole when changing the route of administration from intravenous to oral.

Dosage in adults

1. **Cryptococcal meningitis:** The usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response of the patient this dose may

be increased to 400 mg daily. Usually, duration of treatment for cryptococcal meningitis is 6 – 8 weeks.

For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient has received a full course of primary therapy, FLUCONAZOLE FRESENIUS may be administered at a daily dose of 100 to 200 mg until the CD4 count has stabilised at more than 250 cells/mm^3.

2. **Systemic candidiasis:** The usual dose is 400 mg on the first day followed by 200 mg daily. Depending on the clinical response, the dose may be increased to 400 mg daily. Duration of treatment is based upon the clinical response.
3. **Oropharyngeal candidiasis:** The usual dose is 50 to 100 mg once daily for 7 - 14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function.

   For the prevention of relapse of oropharyngeal candidiasis in patients with AIDS, after the patient has received a full course of primary therapy, FLUCONAZOLE FRESENIUS may be administered at a 150 mg once weekly dose.

   Oesophageal candidiasis: The recommended dose is 200 mg on the first day, followed by 100 mg to 200 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with oesophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.
4. **Prophylaxis against candidiasis:** The recommended FLUCONAZOLE FRESENIUS dosage for the prevention of candidiasis is 50 mg to 400 mg once daily, based on the patient's risk for developing fungal infection.

   For patients at high risk of systemic infection e.g. patients who are anticipated to have profound or prolonged neutropenia, a dose of 400 mg once daily has been used. FLUCONAZOLE FRESENIUS administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1 000 cells per mm^3.

Dosage in elderly

Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance < 50 mL/min) the dosage schedule should be adjusted as described below.

Dosage in renal impairment

Fluconazole is predominantly excreted in the urine as unchanged active substance. No adjustments in single dose therapy are necessary. In patients (including the paediatric population) with impaired renal function who will receive multiple doses of FLUCONAZOLE FRESENIUS, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial dose, the daily dose (according to indication) should be based on the following table:

Dosage and administration of FLUCONAZOLE FRESENIUS	
Creatinine clearance (mL/min)	**Percent of recommended dose**
> 50	100 %
≤ 50 (no dialysis)	50 %
Regular dialysis	100 % after each dialysis

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

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.
The patient's creatine clearance can be estimated from the serum creatinine determination in µmol/L using the modified formula of Cockcroft and Gault:

Males:

$$\text{Creatinine clearance } CL_{cr} \text{ (mL/min):} = \frac{\text{Bodyweight (kg) x (140 – age in years)}}{\text{Serum creatinine level } (S_{cr} \text{ in } \mu\text{mol/L})}$$

For females multiply the answer by 0,85.

Dosage in children

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. The maximum adult daily dosage should not be exceeded in children. FLUCONAZOLE FRESENIUS is administered as a single daily dose.

1. The recommended dosage of FLUCONAZOLE FRESENIUS for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.
2. For the treatment of oesophageal candidiasis, the recommended dosage of FLUCONAZOLE FRESENIUS in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/day may be used based on medical judgment of the patient's response to therapy. Patients with oesophageal candidiasis should be treated for a minimum of three weeks and for at least 2 weeks following the resolution of symptoms.
3. For the treatment of systemic candidiasis and cryptococcal infection, the recommended dosage is 6 - 12 mg/kg/day, depending on the severity of the disease.
4. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 - 12 mg/kg daily, depending on the extent and

duration of the induced neutropenia. For children with impaired renal function, see '**Dosage in renal impairment'** above.

For children with impaired renal function the daily dose should be reduced in accordance with the guidelines given for adults, dependent on the degree of renal impairment.

Dosage in children 4 weeks of age and younger

Neonates excrete FLUCONAZOLE FRESENIUS slowly. In the first two weeks of life the same mg/kg dosing as in older children should be used but administered every 72 hours. During weeks 3 and 4 of life the same dose should be given every 48 hours.

Method of administration

Only for intravenous use as infusion.

FLUCONAZOLE FRESENIUS may be infused at a maximum rate of approximately 200 mg/hour through an existing line with one of the fluids listed in section 6.6.

4.3 Contraindications

- Hypersensitivity to fluconazole or other azole compounds or to any of the excipients of FLUCONAZOLE FRESENIUS (listed in section 6.1).
- Co-administration of terfenadine is contraindicated in patients receiving FLUCONAZOLE FRESENIUS at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. FLUCONAZOLE FRESENIUS should not be co-administered with medicines both known to prolong the QT-interval and metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine (see sections 4.4 and 4.5).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Tinea capitis

FLUCONAZOLE FRESENIUS should not be used for *tinea capitis*.

Cryptococcosis

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

Renal system

FLUCONAZOLE FRESENIUS should be used with caution in patients with renal dysfunction (see section 4.2).

Adrenal insufficiency

FLUCONAZOLE FRESENIUS may cause adrenal insufficiency relating to concomitant treatment with prednisone (see section 4.5, "**The effect of FLUCONAZOLE FRESENIUS on the metabolism of other medicines"**).

Ketoconazole is known to cause adrenal insufficiency and this could also, although less frequently seen, be applicable to FLUCONAZOLE FRESENIUS.

Hepatobiliary system

FLUCONAZOLE FRESENIUS should be administered with caution to patients with liver dysfunction.

FLUCONAZOLE FRESENIUS has been associated with cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of FLUCONAZOLE FRESENIUS-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed.

Hepatotoxicity may be reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during FLUCONAZOLE FRESENIUS therapy should be

monitored for the development of more serious hepatic injury. The patient should be informed of suggestive symptoms of serious hepatic effect (asthenia, anorexia, persistent nausea, vomiting and jaundice). FLUCONAZOLE FRESENIUS should be discontinued immediately if clinical signs or symptoms consistent with liver disease develop that may be attributable to FLUCONAZOLE FRESENIUS, and the patient should consult a medical practitioner.

Dermatological reactions

Patients have less frequently developed pruritus, rashes, urticaria, angioedema, dry skin, abnormal odour, exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis during treatment with FLUCONAZOLE FRESENIUS. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. AIDS patients are more prone to the development of severe cutaneous reaction to many medicines. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and FLUCONAZOLE FRESENIUS discontinued if bullous lesions or erythema multiforme develop.

Hypersensitivity

Anaphylaxis has been reported with the use of FLUCONAZOLE FRESENIUS (see sections 4.3 and 4.8).

Cardiovascular system

FLUCONAZOLE FRESENIUS has been associated with changes on the electrocardiogram such as QT prolongation and *torsades de pointes*.

FLUCONAZOLE FRESENIUS causes QT prolongation via the inhibition of Rectifier Potassium Channel current (I_{kr}). The QT prolongation caused by other medicines (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. There have been cases of QT prolongation and *torsades de pointes* in patients receiving

FLUCONAZOLE FRESENIUS. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medicines that may have been contributory. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular dysrhythmias and *torsades de pointes*.

FLUCONAZOLE FRESENIUS should be administered with caution to patients with these potentially pro-dysrhythmic conditions. Co-administration of other medicines known to prolong the QT-interval and which are metabolised via 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 FRESENIUS and halofantrine is therefore not recommended (see section 4.5).

Cytochrome P450

FLUCONAZOLE FRESENIUS is a moderate CYP2C9 and CYP3A4 inhibitor.

FLUCONAZOLE FRESENIUS is also a strong inhibitor of CYP2C19. FLUCONAZOLE FRESENIUS treated patients who are concomitantly treated with medicines with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).

Terfenadine

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

Porphyria

FLUCONAZOLE FRESENIUS is classified as probably porphyrinogenic.

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 FRESENIUS (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, healthcare providers are advised to take into account the prevalence of resistance in various *Candida* species to FLUCONAZOLE FRESENIUS.

FLUCONAZOLE FRESENIUS contains sodium

FLUCONAZOLE FRESENIUS contains 0,15 mmol sodium per mL and should be taken into consideration for patients on a controlled sodium diet.

1 mL of solution for infusion contains 0,15 mmol (3,5 mg) sodium (as chloride), equivalent to 0,175 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

50 mL solution for infusion contains 7,7 mmol (177 mg) sodium (as chloride), equivalent to 8,85 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

100 mL solution for infusion contains 15,4 mmol (354 mg) sodium (as chloride), equivalent to 17,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

200 mL solution for infusion contains 30,8 mmol (709 mg) sodium (as chloride), equivalent to 35,45 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

The following combinations are contraindicated:

Cisapride (CYP3A4 substrate): Cardiovascular effects, including *torsades de pointes*, have been reported in patients having received concomitant treatment with FLUCONAZOLE FRESENIUS and cisapride. Administration of 200 mg FLUCONAZOLE FRESENIUS once daily concomitantly with cisapride 20 mg four times daily, led to a significant increase in plasma levels of cisapride and prolongation of the QTc-interval. Concurrent treatment with FLUCONAZOLE FRESENIUS and cisapride is contraindicated (see section 4.3).

Terfenadine: Serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, may occur. FLUCONAZOLE FRESENIUS taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of FLUCONAZOLE FRESENIUS at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The co-administration of FLUCONAZOLE FRESENIUS at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of FLUCONAZOLE FRESENIUS with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and *torsades de pointes*. Co-administration of FLUCONAZOLE FRESENIUS and astemizole is contraindicated (see section 4.3).

Pimozide: Concomitant administration of FLUCONAZOLE FRESENIUS with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and *torsades de pointes*. Co-administration of FLUCONAZOLE FRESENIUS and pimozide is contraindicated (see section 4.3).

Quinidine: Concomitant administration of FLUCONAZOLE FRESENIUS with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT

prolongation and *torsades de pointes*. Co-administration of FLUCONAZOLE FRESENIUS and quinidine is contraindicated (see section 4.3).

Erythromycin: Concomitant use of FLUCONAZOLE FRESENIUS and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden death. Co-administration of FLUCONAZOLE FRESENIUS and erythromycin is contraindicated (see section 4.3).

The following combination cannot be recommended:

Halofantrine (CYP3A4 substrate): FLUCONAZOLE FRESENIUS inhibits CYP3A4 and can lead to inhibition of halofantrine metabolism with an increase in halofantrine plasma concentration. Concomitant use of FLUCONAZOLE FRESENIUS and halofantrine has the potential to increase the risk of cardiotoxicity (prolongation of the QT-interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

The following combination should be used with caution:

Amiodarone: Concomitant administration of FLUCONAZOLE FRESENIUS with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of FLUCONAZOLE FRESENIUS and amiodarone is necessary, notably with high dose FLUCONAZOLE FRESENIUS (800 mg) (see section 4.4).

The following medicines should be used with caution, with possible dose adjustments, when administered concomitantly with FLUCONAZOLE FRESENIUS:

The effects of other medicines on FLUCONAZOLE FRESENIUS

Hydrochlorothiazide: In a pharmacokinetic interaction study with healthy volunteers who concomitantly received FLUCONAZOLE FRESENIUS and multiple doses of hydrochlorothiazide the plasma concentrations of FLUCONAZOLE FRESENIUS increased

by 40 %. An effect of this magnitude may necessitate a change in the FLUCONAZOLE FRESENIUS dose in patients who are concomitantly treated with diuretics.

Rifampicin (CYP450 inducer): Concomitant treatment with FLUCONAZOLE FRESENIUS and rifampicin reduced the AUC for FLUCONAZOLE FRESENIUS by 25 % and shortened the half-life of FLUCONAZOLE FRESENIUS by 20 %. An increase in the dose of FLUCONAZOLE FRESENIUS should be considered in combination treatment.

The effect of FLUCONAZOLE FRESENIUS on the metabolism of other medicines

FLUCONAZOLE FRESENIUS is a moderate inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 3A4. FLUCONAZOLE FRESENIUS is also a strong inhibitor of the isoenzyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other medicines metabolised by CYP2C9, CYP2C19 and CYP3A4 co-administered with FLUCONAZOLE FRESENIUS. Therefore, caution should always be observed during combination therapy with such medicines and the patient closely monitored. The enzyme inhibiting effects may persist for 4 – 5 days after discontinuation of FLUCONAZOLE FRESENIUS treatment due to the long half-life of fluconazole.

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

Alfentanil (CYP3A4 substrate): On simultaneous intravenous administration of 400 mg FLUCONAZOLE FRESENIUS and 20 microgram/kg alfentanil to healthy volunteers, the AUC_{10} of alfentanil increased two-fold and clearance decreased by 55 %, probably through inhibition of CYP3A4. The combination may require dose adjustment of alfentanil.

Amitriptyline/Nortriptyline: Several case reports have described the development of elevated amitriptyline concentrations and signs of tricyclic toxicity when amitriptyline is used in combination with FLUCONAZOLE FRESENIUS. Concomitant infusion of FLUCONAZOLE FRESENIUS and nortriptyline, the active metabolite of amitriptyline, has been reported to lead to increased nortriptyline levels. Due to the risk of amitriptyline toxicity, monitoring of amitriptyline levels should be considered with dose adjustment where indicated. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericin B: Concurrent administration of FLUCONAZOLE FRESENIUS 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 medicines in systemic infection with *Aspergillus fumigatus*. The clinical significance of these results is unknown.

Anticoagulants (CYP2C9 substrate): In concomitant treatment with FLUCONAZOLE FRESENIUS and warfarin, the prothrombin time/INR increased up to two-fold causing bleeding events such as bruising, epistaxis, gastrointestinal bleeding, haematuria and melena. This is probably due to an inhibition of the metabolism of warfarin via CYP2C9. The prothrombin time/INR should be monitored closely in patients treated concomitantly with FLUCONAZOLE FRESENIUS and coumarin-type anticoagulants, such as warfarin, or indanedione anticoagulants. Dose adjustment of warfarin may be necessary.

Azithromycin: There is no significant pharmacokinetic interaction between FLUCONAZOLE FRESENIUS and azithromycin.

Antiretroviral medicines (CYP3A4 substrate): There are reports of increased serum levels following concurrent administration of FLUCONAZOLE FRESENIUS with antiretroviral medicines such as nevirapine.

- *Zidovudine:* Interaction studies have shown that when zidovudine is taken together with FLUCONAZOLE FRESENIUS 200 mg or 400 mg daily the zidovudine C_{max} and AUC values may be raised by between 84 % and 74 % respectively probably as a result of the inhibition of conversion to the glucuronide and approximately 45 % decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128 % following combination therapy with FLUCONAZOLE FRESENIUS. Patients receiving this combination should be monitored for zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.
- *Saquinavir:* FLUCONAZOLE FRESENIUS increases the AUC and C_{max} of saquinavir with approximately 50 % and 55 % respectively, and decreases the clearance of saquinavir by approximately 50 %, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dose adjustment of saquinavir may be necessary.

Short acting benzodiazepines (CYP3A4 substrate): FLUCONAZOLE FRESENIUS may inhibit the metabolism of benzodiazepines metabolised via CYP3A4, e.g. midazolam and triazolam. In concomitant oral single dose treatment with fluconazole (400 mg) and midazolam (7,5 mg) AUC increased 3,7 times and the half-life of midazolam 2,2 times. The combination should be avoided. Where concomitant treatment is considered necessary, a reduction in the dose of midazolam should be considered and the patient monitored closely. In concomitant treatment with FLUCONAZOLE FRESENIUS (100 mg daily for 4 days) and triazolam (0,25 mg) the AUC and half-life of triazolam increased respectively 2,5 and 1,8 times. Prolonged and enhanced effects from triazolam have been observed. The combination may require reduction in the dose of triazolam.

Calcium channel blockers (CYP3A4 substrate): Some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, verapamil, nicardipine, amlodipine, and felodipine are metabolised via CYP3A4. FLUCONAZOLE FRESENIUS has the potential to increase the systemic exposure of the calcium channel blockers. Frequent monitoring for adverse events is recommended.

Carbamazepine (CYP3A4 substrate): FLUCONAZOLE FRESENIUS inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30 % has been observed. There is a risk of carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Celecoxib (CYP2C9 substrate): In concomitant treatment with FLUCONAZOLE FRESENIUS (200 mg daily) and celecoxib (200 mg), C_{max} and AUC for celecoxib increased by 68 % and 134 % respectively. A 50 % reduction of the dose of celecoxib is recommended in combination therapy with FLUCONAZOLE FRESENIUS.

Ciclosporin (CYP3A4 substrate): FLUCONAZOLE FRESENIUS significantly increases the concentration and AUC of ciclosporin. The plasma concentration of ciclosporin should be monitored in concomitant treatment with FLUCONAZOLE FRESENIUS. The dose of ciclosporin may be reduced.

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

Didanosine: Co-administration of didanosine and FLUCONAZOLE FRESENIUS appears to be safe and has little effect on didanosine pharmacokinetics or efficacy. However, it is important to monitor the FLUCONAZOLE FRESENIUS response. It may be advantageous to stagger FLUCONAZOLE FRESENIUS dosing to a time prior to didanosine administration.

Endogenous steroids: No adverse effect has been seen on endogenous steroid levels or on ACTH stimulated cortisol response.

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

Fentanyl: One fatal case of possible fentanyl FLUCONAZOLE FRESENIUS interaction was reported. The author judged that the patient died from fentanyl intoxication. Fentanyl elimination may be delayed significantly by FLUCONAZOLE FRESENIUS, leading 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 (CYP2C9- or CYP3A4 substrate): The risk of myopathy and rhabdomyolysis increases when FLUCONAZOLE FRESENIUS is administered concomitantly with HMG-CoA reductase inhibitors that are metabolised via CYP3A4 e.g. atorvastatin or simvastatin, or by CYP2C9 such as fluvastatin. For fluvastatin an individual increase of up to 200 % in the area under the curve (AUC) can occur as a result of interaction between fluvastatin and FLUCONAZOLE FRESENIUS. An individual patient using fluvastatin 80 mg daily may be exposed to considerable fluvastatin concentrations if treated with high doses of FLUCONAZOLE FRESENIUS. Caution should be observed where concomitant treatment with FLUCONAZOLE FRESENIUS and HMG-CoA reductase inhibitors is considered necessary.

The combination may require dose reduction of the HMG-CoA-reductase inhibitors. Patients should be observed with regard to signs of myopathy or rhabdomyolysis and creatine kinase levels (CK). The HMG-CoA treatment 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 FRESENIUS 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 medicines in the same therapeutic class): Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1,9-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

Losartan (CYP2C9 substrate): FLUCONAZOLE FRESENIUS inhibits the conversion of losartan to its active metabolite (E-3174), which is responsible for most of the angiotensin II receptor antagonism that occurs with losartan therapy. Simultaneous treatment with FLUCONAZOLE FRESENIUS may lead to increased losartan concentrations and decreased concentrations of the active metabolite. It is recommended that the blood pressure of the patients receiving the combination should be monitored regularly.

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

Methadone (CYP3A4 substrate): There have been reports of an intensified effect of methadone after simultaneous administration of FLUCONAZOLE FRESENIUS and methadone. One pharmacokinetic study showed an average increase in the AUC of methadone by 35 %. Dosage adjustment of methadone may be necessary with combined therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs): The C_{max} and AUC of flurbiprofen may be increased by about 23 % and 81 %, respectively, when co-administered with FLUCONAZOLE FRESENIUS compared to administration of flurbiprofen alone. The C_{max} and AUC of ibuprofen may be similarly increased.
FLUCONAZOLE FRESENIUS has the potential to increase the systemic exposure of other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for side effects and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Olaparib: Moderate inhibitors of CYP3A4 such as FLUCONAZOLE FRESENIUS 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.

Oral contraceptives: FLUCONAZOLE FRESENIUS given at 50 mg daily had no relevant effects on hormone levels of combined oral contraceptives. FLUCONAZOLE FRESENIUS given at 200 mg daily may raise the AUC of ethinylestradiol and levonorgestrel by about 40 % and 24 % respectively. Multiple dose use of FLUCONAZOLE FRESENIUS at these doses is therefore unlikely to influence the effect of the combined oral contraceptive.

Phenytoin (CYP2C9 substrate): Intravenous administration of 200 mg FLUCONAZOLE FRESENIUS together with 250 mg phenytoin may increase the AUC_{24} and the C_{min} of

phenytoin by 75 % and 128 %, respectively. In combination treatment, plasma phenytoin concentrations should be monitored and the dose adjusted in order to avoid phenytoin toxicity.

Prednisone (CYP3A4 substrate that is metabolised to prednisolone): A liver transplant recipient receiving prednisone experienced an Addisonian crisis when a three-month course of FLUCONAZOLE FRESENIUS was discontinued. Withdrawal of FLUCONAZOLE FRESENIUS probably caused an increase in CYP3A4 activity, so that degradation of prednisone increased. Patients undergoing long-term treatment with FLUCONAZOLE FRESENIUS and prednisone (or other adrenocorticoid therapy) should be closely monitored for signs of adrenal insufficiency when FLUCONAZOLE FRESENIUS is discontinued (see section 4.4).

Rifabutin (CYP3A4 substrate): In concomitant treatment with FLUCONAZOLE FRESENIUS and rifabutin the serum concentrations of rifabutin increase up to 80 %. Uveitis has been reported. Patients undergoing concomitant treatment should be monitored closely.

Sirolimus: FLUCONAZOLE FRESENIUS increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

Sulphonylureas (CYP2C9 substrate): FLUCONAZOLE FRESENIUS has displayed prolonged half-life in serum for concomitantly administered sulphonylureas (glibenclamide, glipizide, chlorpropamide and tolbutamide) in healthy volunteers. FLUCONAZOLE FRESENIUS may be administered to diabetics together with sulphonylureas, but the risk of hypoglycaemia should be considered. Blood glucose levels should be closely monitored and appropriate reduction of sulfonylurea dosage is recommended during co-administration.

Tacrolimus (CYP3A4 substrate): In concomitant oral treatment with fluconazole and tacrolimus (0,15 mg/kg twice daily) the plasma concentration trough level of tacrolimus increased 1,4 and 3,1 times with a daily fluconazole dose of 100 mg and 200 mg respectively. Nephrotoxicity has been reported. In concomitant treatment with FLUCONAZOLE FRESENIUS and tacrolimus, patients should be closely monitored and an adjustment in dose considered.

Theophylline: Administration of 200 mg FLUCONAZOLE FRESENIUS for 14 days led to an 18 % decrease in the mean plasma clearance of theophylline. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving FLUCONAZOLE FRESENIUS, and the therapy modified appropriately if signs of toxicity develop.

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

Tolvaptan: Exposure to tolvaptan is significantly increased (200 % in AUC; 80 % in C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with FLUCONAZOLE FRESENIUS, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions; particularly 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.

Trimetrexate: FLUCONAZOLE FRESENIUS may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity (bone marrow suppression, renal and hepatic dysfunction, and gastrointestinal ulceration) must be closely monitored.

Vinca alkaloids: Although not studied, FLUCONAZOLE FRESENIUS 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 FRESENIUS, central nervous system (CNS) related side effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of FLUCONAZOLE FRESENIUS treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: Voriconazole is a CYP2C9, CYP2C19 and CYP3A4 inhibitor. Co-administration of oral voriconazole and oral fluconazole results in an increase in C_{max} and area under the curve (AUC) of voriconazole by an average of 57 % and 79 % respectively. Concomitant administration of voriconazole and FLUCONAZOLE FRESENIUS at any dose is not recommended. Monitoring for voriconazole associated side effects is recommended if voriconazole is used sequentially after FLUCONAZOLE FRESENIUS.

Xanthine bases, other antiepileptic medicines and isoniazid: Follow-up tests must be carried out when FLUCONAZOLE FRESENIUS is administered concomitantly with xanthine bases, other antiepileptic medicines and isoniazid.

Other interactions with medicines

Medicines that cause QT prolongation:

Case reports indicate that FLUCONAZOLE FRESENIUS may induce QT prolongation leading to serious cardiac dysrhythmia (see sections 4.3 and 4.4).

Drug-drug interaction studies with other medicines have not been conducted, but such interactions may occur.

4.6 Fertility, pregnancy and lactation

FLUCONAZOLE FRESENIUS is contraindicated in pregnancy and lactation (see section 4.3).

Women of childbearing potential / contraception in males and females

Before initiating treatment, the patient should be informed of the potential risk to the foetus.

After single dose treatment, a washout period of 1 week (corresponding to 5-6 half-lives) is recommended before becoming pregnant (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 FRESENIUS during the first and/or second trimester compared to women not treated with fluconazole or treated with topical azoles during the same period.

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**.**

Breastfeeding

Fluconazole is secreted into breast milk at concentrations similar to those in plasma. FLUCONAZOLE FRESENIUS should not be used in mothers breastfeeding their infants.

Fertility

FLUCONAZOLE FRESENIUS did not affect the fertility of male or female rats.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or seizures (see section 4.8) while receiving FLUCONAZOLE FRESENIUS and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

a) Summary of the safety profile

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

The most frequently reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, and rash.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations			Infection due to resistant microorganisms
Blood and the lymphatic system disorders		Anaemia Agranulocytosis Leukopenia Neutropenia Thrombocytopenia	
Immune system disorders		Anaphylactic reaction Angioedema Facial oedema	
Metabolism and nutrition disorders		Decreased appetite Hypercholesterolaemia Hypertriglyceridaemia Hypokalaemia	
Psychiatric disorders		Insomnia Somnolence	
Nervous system disorders	Headache	Convulsion Seizures Dizziness	

		Paraesthesia Abnormal taste sensation Tremor	
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Ventricular dysrhythmia (QT prolongation, *torsades de pointes*)	
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 ALP, ALT and AST	Cholestasis Total bilirubin increased Jaundice Hepatotoxicity Hepatitis Liver cell necrosis Liver failure with fatal cases*	

Skin and subcutaneous tissue disorders	Maculopapular erythema Rash	Urticaria Pruritus Increased sweating (Fixed) drug eruption Exfoliative skin disorders Stevens-Johnson syndrome Toxic epidermal necrolysis Lyell syndrome Acute generalised exanthematous pustulosis Alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders		Myalgia	
Renal and urinary disorders		Changes in renal function tests	
General disorders and administrative site conditions		Fatigue Malaise Asthenia Fever	

* The appropriate laboratory values should be very closely monitored.

c) Description of selected adverse reactions

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities have been observed during treatment with FLUCONAZOLE FRESENIUS.

d) Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities in the paediatric population are comparable to those in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Symptoms of overdose

There have been reports of overdose with FLUCONAZOLE FRESENIUS accompanied by hallucinations and paranoid behaviour.

Treatment of overdose

In the event of overdose, supportive measures and symptomatic treatment may be adequate.

FLUCONAZOLE FRESENIUS is mainly excreted in the urine. A 3-hour haemodialysis session reduces plasma levels by approximately 50 %. Forced volume diuresis would probably increase the elimination rate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.2 Fungicides.

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.

ATC code: J02AC01

Mechanism of action

Fluconazole belongs to the triazole class of antimycotics, with a mainly fungistatic action. It is a selective inhibitor of ergosterol synthesis in fungi, which leads to defects in the cell membrane. Fluconazole is very specific for fungal cytochrome P450 dependant enzymes.

Resistance

There have been reports of superinfection with *Candida* species other than *C. albicans*, which are inherently not susceptible to fluconazole (e.g. *C. kruisei*). Such cases may require alternative antifungal therapy.

5.2 Pharmacokinetic properties

Absorption

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

Fluconazole is well absorbed after oral intake. The absolute bioavailability is greater than 90 %. Oral absorption is not affected by simultaneous food intake. The maximum fasting

plasma concentration is reached 0,5 -1,5 h after administration of the dose. 90 % of the steady-state level is reached 4 - 5 days after dosing once daily.

The plasma concentration is proportional to the dose. After administration of 200 mg fluconazole, C_{max} is approx. 4,6 mg/L and the plasma steady-state concentrations after 15 days are about 10 mg/L. After administration of 400 mg fluconazole, C_{max} is approx. 9 mg/L and the plasma steady-state concentrations after 15 days are about 18 mg/L. Taking a double dose on day 1 leads to plasma concentrations of approx. 90 % of the plasma steady-state concentrations on day 2.

Distribution

The apparent volume of distribution of fluconazole corresponds to total body water. Binding to plasma proteins is low (11 % - 12 %).

Fluconazole achieves good penetration into all body fluids studied. The fluconazole concentrations in saliva and sputum are comparable to the plasma concentrations. In patients with fungal meningitis the fluconazole concentrations in cerebrospinal fluid (CSF) are approx. 80 % of the corresponding plasma concentrations.

Biotransformation

Fluconazole is broken down to a modest extent. Only 11 % of a radioactive dose is excreted in the form of metabolites in the urine.

Elimination

Fluconazole is mainly excreted via the kidneys. Approximately 80 % of the dose is excreted in non-metabolised form in the urine. Fluconazole clearance is proportional to the creatinine clearance. There is no evidence of circulating metabolites, but accumulation is significant over 15 days and concentrations may rise 2 - 3 fold.

The mean half-life in the plasma is approx. 30 h. The long plasma half-life provides the basis for treatment with single daily doses in all indications.

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR < 20 mL/min) the 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 a haemodialysis session, around 50 % of fluconazole is eliminated from the blood.

Pharmacokinetics in children

Pharmacokinetic studies performed in children have shown that fluconazole is cleared faster in children than in adults and a shorter fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose in children. This is comparable with the fluconazole plasma elimination half-life after single administration of 3 mg/kg IV to children of 11 days – 11 months old. The distribution volume in this age group was about 950 mL/kg.

In neonates fluconazole, administered every 72 hours, demonstrated a mean half-life of 74 hours over the first 2 weeks of life, which is considerably longer than the adult value. The volume of distribution was found to be about 1 200 mL/kg in neonates.

The pharmacokinetic properties of fluconazole have not been investigated in children with renal insufficiency.

Pharmacokinetics in the 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 medicine recovered unchanged in urine (0-24 hr, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

Hydrochloric acid or sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

FLUCONAZOLE FRESENIUS must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 36 months

After opening: The product must be used immediately after first opening.

After dilution: Dilution is not necessary prior to administration.

For the diluted product chemical and physical stability has been demonstrated for 24 hours at or below 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze. Keep the product in the outer container until required for use.

For storage after opening or dilution, see section 6.3.

6.5 Nature and contents of container

Clear transparent bottlepack polyethylene (KabiPac) containers packed in 50 mL; 100 mL and 200 mL bottles.

50 mL solution filled in 100 mL clear transparent polyethylene bottlepack container with cap and bromobutyl rubber disc with a hanger at the bottom.

100 mL solution filled in 100 mL clear transparent polyethylene bottlepack container with cap and bromobutyl rubber disc with a hanger at the bottom.

200 mL solution filled in 250 mL clear transparent polyethylene bottlepack container with cap and bromobutyl rubber disc with a hanger at the bottom.

Pack sizes of 1, 10; 20; 25; 30; 40 or 60 bottles.

Not all listed container sizes and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

FLUCONAZOLE FRESENIUS intravenous infusion is compatible with the following administration fluids. Mixing with any other medicine prior to infusion is not recommended:

a) Dextrose 20 %

b) Ringer's solution

c) Ringer-lactate

d) Potassium chloride dextrose 5 %

e) Sodium bicarbonate 4,2 %

f) Sodium chloride 0,9 % (normal saline)

FLUCONAZOLE FRESENIUS is for single use only. Discard remaining contents after use.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand no. 7, Growthpoint Business Park

162 Tonetti Street

Halfway House extension 7, Midrand, 1685

South Africa

Telephone number: (011) 545 0000

8. REGISTRATION NUMBER

46/20.2.2/0312

9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION

29 September 2017

10. DATE OF REVISION OF THE TEXT

13 February 2025