BIO FLUCONAZOLE IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BIO FLUCONAZOLE IV 200 mg fluconazole per 100 mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL solution contains 200 mg fluconazole (2 mg/mL).
Sugar free.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
A clear colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Once the results of the cultures and other laboratory studies become available, anti-infective therapy should be adjusted.
BIO FLUCONAZOLE IV is indicated for the treatment of the following conditions in adults:
– Cryptococcal meningitis in mentally alert patients without localising neurological signs and as a follow up therapy after Amphotericin B therapy.
– Maintenance therapy to prevent relapse of cryptococcal disease in patients with acquired immunodeficiency syndrome (AIDS).
– Systemic candidiasis.
– Oropharyngeal and oesophageal candidiasis.
– Prophylaxis of fungal infections in patients receiving cytotoxic chemotherapy and/or radiation therapy.
– Vaginal candidiasis – Acute or recurrent infections and as prophylaxis to reduce the incidence of recurrent infections.
– Candidial balanitis.
– Dermatomycosis including *tinea pedis, tinea corporis, tinea cruris, tinea unguium* (onychomycosis) and dermal candida infections.

BIO FLUCONAZOLE IV is indicated for the treatment of the following conditions in children:
– Cryptococcal meningitis in mentally alert patients without localising neurological signs and as a follow up therapy after Amphotericin B therapy.
– Maintenance therapy to prevent relapse of cryptococcal disease in patients with acquired immunodeficiency syndrome (AIDS).
– Systemic candidiasis.
– Oropharyngeal and oesophageal candidiasis.
– Prophylaxis of candidiasis in patients receiving cytotoxic chemotherapy and/or radiation therapy.

4.2 Posology and method of administration

The daily dose of BIO FLUCONAZOLE IV should be based on the nature and severity of the fungal infection.
Therapy for those types of infections requiring multiple dose treatment 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.
Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

Use in adults:

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, the duration of treatment for cryptococcal meningitis is 6 to 8 weeks.

Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with AIDS
After the patient receives a full course of primary therapy, BIO FLUCONAZOLE IV may be administered at a daily dose of 100 mg to 200 mg until the CD4 count has stabilised at more than 250 cells/mm^3.

Systemic candidiasis
The usual dose is 400 mg on the first day followed by 200 mg. Depending on the clinical response, the dose may be increased to 400 mg daily. Duration of treatment is based on clinical and mycological response.

Oropharyngeal candidiasis
The usual dose is 50 mg to 100 mg once daily for 7 to 14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function.
To prevent relapse in AIDS patients, after the patient receives a full course of primary therapy, BIO FLUCONAZOLE IV 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 once a day may be used, based on medical judgment of the patient's response to therapy. Duration of treatment is a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms.

Prophylaxis of fungal infections in patients who receive cytotoxic chemotherapy and/or radiation therapy
The recommended dose is 50 mg to 400 mg once daily depending on the patient's risk for developing fungal infections. 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. Treatment 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.

Vaginal candidiasis
150 mg administered as a single dose.

Recurrent vaginal candidiasis
150 mg administered as a single dose, once a month. The duration of therapy should be individualised but ranges from 4 to 12 months. Some patients may require more frequent dosing.

Candida balanitis
150 mg administered as a single dose.

Dermal infections including tinea pedis, tinea corporis, tinea cruris, tinea unguium (onychomycosis) and dermal candida infections
The recommended dose is 150 mg administered as a single dose once a week. Duration of treatment is usually 2 to 4 weeks but *tinea pedis* may require up to 6 weeks of treatment. For *tinea unguium* treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally require 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.

Special populations:

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.

Renal impairment
BIO FLUCONAZOLE IV is cleared primarily by renal excretion as unchanged medicine. No adjustments in single dose therapy are necessary. Multiple-dose therapy should be carefully monitored in patients with renal impairment.
In patients (including children) with impaired renal function, an initial dose of 50 mg to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine clearance (mL/min)	**BIO FLUCONAZOLE IV Percent of recommended dose**
> 50	100 %
≤ 50 (no dialysis)	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.

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition. When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance:

Males:

$$\frac{(140 - \text{age}) \times \text{Wt (kg)} \times \text{constant}}{S_{cr}\ (\text{mmol/L})}$$

Constant = 1,23 for males
S_{cr} = serum creatinine
Females:

$$\frac{(140 - \text{age}) \times \text{Wt (kg)} \times \text{constant}}{S_{cr}\ (\text{mmol/L})}$$

Constant = 1,04 for females (0,85 x 1,23 = 1,04)
S_{cr} = serum creatinine

Paediatric population

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. BIO FLUCONAZOLE IV is administered as a single daily dose.
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.

Cryptococcal meningitis
The recommended dose is 6 mg/kg/day to 12 mg/kg/day, depending on the severity of the disease.

Systemic candidiasis
The recommended dose is 6 mg/kg/day to 12 mg/kg/day, depending on the severity of the disease.

Oropharyngeal candidiasis
The recommended dose 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.

Oesophageal candidiasis
The recommended dose 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. Duration of treatment is for a minimum of 3 weeks and for at least 2 weeks following the resolution of symptoms.

Prophylaxis of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy
The recommended dose is 3 to 12 mg/kg/day depending on the extent and duration of the induced neutropenia.

Use in children 4 weeks of age and younger
Neonates excrete BIO FLUCONAZOLE IV slowly. In the first 2 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

BIO FLUCONAZOLE IV 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.
BIO FLUCONAZOLE IV is formulated in 0,9 % sodium chloride solution, each 200 mg (100 mL bottle) containing 15 mmol each of sodium (Na^+) and chloride (Cl^-) ions. Because BIO FLUCONAZOLE IV is available as a dilute saline solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.
For instructions on dilution of BIO FLUCONAZOLE IV infusion before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to fluconazole or to related azole medicines, or to any of the excipients listed in section 6.1.
- Co-administration of terfenadine is contraindicated in patients receiving BIO FLUCONAZOLE IV at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Co-administration of other medicines 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 BIO FLUCONAZOLE IV (see sections 4.4 and 4.5).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Hepatobiliary system
BIO FLUCONAZOLE IV should be administered with caution to patients with liver dysfunction.
BIO FLUCONAZOLE IV has been associated with cases of serious hepatotoxicity, including fatalities related to dose and duration of use, primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Hepatotoxicity may be reversible on discontinuation of therapy.
Patients who develop abnormal liver function tests during BIO FLUCONAZOLE IV therapy should be monitored for the development of more serious hepatic injury. The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). BIO FLUCONAZOLE IV should be discontinued if clinical signs or symptoms consistent with the liver disease develop that may be attributable to BIO FLUCONAZOLE IV.

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 BIO FLUCONAZOLE IV. 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 a rash, which is considered attributable to BIO FLUCONAZOLE IV, develops in a patient treated for a superficial fungal infection, further therapy with BIO FLUCONAZOLE IV should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely, and BIO FLUCONAZOLE IV discontinued if bullous lesions or erythema multiforme develop.

Hypersensitivity
Anaphylaxis has been reported with the use of fluconazole as contained in BIO FLUCONAZOLE IV (see section 4.8).

Cardiovascular system
Certain azoles, including fluconazole as contained in BIO FLUCONAZOLE IV, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicines (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. During post-marketing surveillance, there have been cases of QT prolongation and torsades de pointes in patients taking fluconazole as contained in BIO FLUCONAZOLE IV. 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 hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular dysrhythmias and torsades de pointes.
BIO FLUCONAZOLE IV should be administered with caution in patients with potentially prodysrhythmic conditions. Co administration of other medicines 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 BIO FLUCONAZOLE IV and halofantrine is therefore not recommended (see section 4.5).

Renal system
BIO FLUCONAZOLE IV should be administered with caution to patients with renal dysfunction (see section 4.2).

Adrenal insufficiency
DIFLUCAN may cause adrenal insufficiency relating to concomitant treatment with prednisone (see section 4.5, "The effect of BIO FLUCONAZOLE IV on other medicines").

Cytochrome P450
Fluconazole as contained in BIO FLUCONAZOLE IV, is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. BIO FLUCONAZOLE IV-treated patients who are concomitantly treated with medicines with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4 should be monitored (see sections 4.3 and 4.5).

Terfenadine
The co administration of BIO FLUCONAZOLE IV at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

Candidiasis
Studies have shown an increasing prevalence of infections with Candida species other than *C. albicans*. These are often inherently resistant (e.g., *C. krusei* and *C. auris*) or show reduced susceptibility to fluconazole as contained in BIO FLUCONAZOLE IV (*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 BIO FLUCONAZOLE IV.

BIO FLUCONAZOLE IV contains sodium
BIO FLUCONAZOLE IV contains 354 mg (15,4 mmol) sodium per 100 mL dose, equivalent to 17,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
The maximum daily dose of BIO FLUCONAZOLE IV is equivalent to 35,4 % of the WHO recommended maximum daily intake for sodium.
BIO FLUCONAZOLE IV is considered high in sodium. This should be particularly taken into account when it is administered to patients on a low salt diet.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of the following other medicines is contraindicated

Cisapride
There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole as contained in BIO FLUCONAZOLE IV, and cisapride were co administered. In a controlled study it was 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 cisapride is contraindicated in patients receiving BIO FLUCONAZOLE IV (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 as contained in BIO FLUCONAZOLE IV, failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole as contained in BIO FLUCONAZOLE IV, 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 BIO FLUCONAZOLE IV at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The co administration of BIO FLUCONAZOLE IV at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole
Concomitant administration of fluconazole as contained in BIO FLUCONAZOLE IV, 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 BIO FLUCONAZOLE IV and astemizole is contraindicated (see section 4.3).

Pimozide
Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole as contained in BIO FLUCONAZOLE IV, 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 BIO FLUCONAZOLE IV and pimozide is contraindicated (see section 4.3).

Quinidine
Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole as contained in BIO FLUCONAZOLE IV, 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 BIO FLUCONAZOLE IV and pimozide is contraindicated (see section 4.3).

Erythromycin
Concomitant use of fluconazole as contained in BIO FLUCONAZOLE IV, and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. Co administration of BIO FLUCONAZOLE IV and erythromycin is contraindicated (see section 4.3).

Concomitant use of the following other medicines cannot be recommended

Halofantrine
Fluconazole as contained in BIO FLUCONAZOLE IV, can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of BIO FLUCONAZOLE IV 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 that should be used with caution

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

Concomitant use of the following other medicines lead to precautions and dose adjustments

Hydrochlorothiazide
In a pharmacokinetic interaction study, co administration of multiple dose hydrochlorothiazide to healthy volunteers receiving fluconazole as contained in BIO FLUCONAZOLE IV, increased plasma concentration of fluconazole by 40 %. An effect of this magnitude may not necessitate a change in the BIO FLUCONAZOLE IV dose regimen in subjects receiving concomitant diuretics.

Rifampicin
Concomitant administration with fluconazole as contained in BIO FLUCONAZOLE IV 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 BIO FLUCONAZOLE IV dose should be considered.

The effect of BIO FLUCONAZOLE IV on other medicines
Fluconazole as contained in BIO FLUCONAZOLE IV, is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other medicines metabolised by CYP2C9, CYP2C19 and CYP3A4 co administered with fluconazole. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment, such as BIO FLUCONAZOLE IV, due to the long half-life of fluconazole (see section 4.3).

Alfentanil
A study observed a reduction in clearance and distribution volume as well as prolongation of t½ of alfentanil following concomitant treatment with fluconazole as contained in BIO FLUCONAZOLE IV. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline
Fluconazole as contained in BIO FLUCONAZOLE IV, 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 as contained in BIO FLUCONAZOLE IV, and amphotericin B in infected normal and immunosuppressed mice showed 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 results obtained in these studies is unknown.

Anticoagulants
In an interaction study, fluconazole as contained in BIO FLUCONAZOLE IV has been reported to increase the prothrombin time/international normalised ratio (INR) (12 %) after warfarin administration in healthy males. As with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. A possible mechanism of action is fluconazole's inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type (warfarin) or indanedione anticoagulants concurrently with BIO FLUCONAZOLE IV the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

Azithromycin
There was no significant pharmacokinetic interaction reported between fluconazole as contained in BIO FLUCONAZOLE IV, and azithromycin.

Benzodiazepines (short-acting), i.e. midazolam, triazolam
Following oral administration of midazolam, fluconazole as contained in BIO FLUCONAZOLE IV resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than intravenous administration of fluconazole such as BIO FLUCONAZOLE IV. If concomitant benzodiazepine therapy is necessary in patients being treated with BIO FLUCONAZOLE IV, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.
Fluconazole increases the AUC of triazolam (single dose) by approximately 50 %, C_{max} by 20 32 % and increases t½ by 25 - 50 % due to the inhibition of metabolism of triazolam. Potentiated and prolonged effects of triazolam have been observed with concomitant treatment with fluconazole as contained in BIO FLUCONAZOLE IV. Dose adjustments of triazolam may be necessary.

Carbamazepine
Fluconazole as contained in BIO FLUCONAZOLE IV, 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 antagonists
Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolised by CYP3A4. Fluconazole as contained in BIO FLUCONAZOLE IV 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) as contained BIO FLUCONAZOLE IV, and celecoxib (200 mg), the celecoxib C_{max} and AUC increased by 68 % and 134 %, respectively. Half of the celecoxib dose may be necessary when combined with BIO FLUCONAZOLE IV.

Ciclosporin
Fluconazole as contained in BIO FLUCONAZOLE IV significantly increases the concentration and AUC of ciclosporin. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Cyclophosphamide
Combination therapy with cyclophosphamide and fluconazole as contained in BIO FLUCONAZOLE IV, 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.

Endogenous steroid
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 as contained in BIO FLUCONAZOLE IV may increase serum concentrations of everolimus through inhibition of CYP3A4.

Fentanyl
One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction, was reported. Furthermore, it was shown in healthy volunteers that fluconazole as contained in BIO FLUCONAZOLE IV 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. Dose adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors
The risk of myopathy and rhabdomyolysis increases when fluconazole as contained in BIO FLUCONAZOLE IV, is administered concomitantly with HMG CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed, or myopathy/rhabdomyolysis is diagnosed or suspected.

Ibrutinib
Moderate inhibitors of CYP3A4 such as fluconazole contained in BIO FLUCONAZOLE IV, 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
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 as contained in BIO FLUCONAZOLE IV, and erythromycin.

Losartan
Fluconazole, as contained in BIO FLUCONAZOLE IV, 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 regularly.

Methadone
Fluconazole as contained in BIO FLUCONAZOLE IV may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs (NSAIDs)
The C_{max} and AUC of flurbiprofen was increased by 23 % and 81 %, respectively, when co-administered with fluconazole as contained in BIO FLUCONAZOLE IV, compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15 % and 82 %, respectively, when fluconazole was co-administered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.
Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolised by CYP2C9 (e.g., naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Olaparib
Moderate inhibitors of CYP3A4 such as fluconazole as contained in BIO FLUCONAZOLE IV, 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
Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole as contained in BIO FLUCONAZOLE IV. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinylestradiol and levonorgestrel were increased 40 % and 24 %, respectively. Thus, multiple dose use of BIO FLUCONAZOLE IV at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Phenytoin
Fluconazole as contained in BIO FLUCONAZOLE IV inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone
There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole as contained in BIO FLUCONAZOLE IV, 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 BIO FLUCONAZOLE IV and prednisone should be carefully monitored for adrenal cortex insufficiency when BIO FLUCONAZOLE IV is discontinued (see section 4.4).

Rifabutin
There have been reports that an interaction exists when fluconazole as contained in BIO FLUCONAZOLE IV, is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80 %. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving rifabutin and BIO FLUCONAZOLE IV concomitantly should be carefully monitored.

Saquinavir
Fluconazole, as contained in BIO FLUCONAZOLE IV, increases the AUC of saquinavir with approximately 50 %, C_{max} by approximately 55 % 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.

Sirolimus
Fluconazole as contained in BIO FLUCONAZOLE IV, 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.

Sulfonylureas
Fluconazole, as contained in BIO FLUCONAZOLE IV, has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during co-administration.

Tacrolimus
Fluconazole, as contained in BIO FLUCONAZOLE IV, 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.

Theophylline
In a placebo-controlled interaction study, the administration of fluconazole, as contained in BIO FLUCONAZOLE IV, 200 mg for 14 days resulted in an 18 % decrease in the mean plasma clearance of theophylline, which leads to increased theophylline plasma concentrations and possibly toxicity. 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 BIO FLUCONAZOLE IV, and the therapy modified appropriately if signs of toxicity develop. Theophylline concentrations should be monitored.

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 as contained in BIO FLUCONAZOLE IV). 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 as contained in BIO FLUCONAZOLE IV, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced as instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.

Vinca alkaloids
Although not studied, fluconazole as contained in BIO FLUCONAZOLE IV 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 as contained in BIO FLUCONAZOLE IV, pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. Potential central nervous system (CNS) adverse events should be monitored for when this combination of medicines is used.

Voriconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)
Co administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 2,5 days) and oral fluconazole (400 mg on day 1, then 200 mg every 24 hours for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC of voriconazole by an average of 57 % (90 % CI: 20 %, 107 %) and 79 % (90 % CI: 40 %, 128 %), respectively. It was reported in a follow-on clinical study involving 8 healthy male subjects, that reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. Concomitant administration of voriconazole and BIO FLUCONAZOLE IV at any dose is not recommended.

Zidovudine
Fluconazole as contained in BIO FLUCONAZOLE IV increases C_{max} and AUC of zidovudine by 84 % and 74 %, respectively, due to an approximately 45 % decrease in oral zidovudine clearance. The half life of zidovudine was likewise prolonged by approximately 128 % following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Other information on interactions
Co-administration of fluconazole and nevirapine resulted in approximately 100 % increase in nevirapine exposure as compared with historical data where nevirapine was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if nevirapine and BIO FLUCONAZOLE IV are given concomitantly, and patients should be monitored closely.
Interaction studies have shown that when fluconazole as contained in BIO FLUCONAZOLE IV, is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.
Medical practitioners should be aware that drug-drug interaction studies with other medicines have not been conducted, but such interactions may occur.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential/contraception in males and females
Effective contraceptive measures must be used in women of childbearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.

Pregnancy
BIO FLUCONAZOLE IV is contraindicated for use during pregnancy (see section 4.3).
There have been reports of congenital abnormalities in infants whose mothers were treated with fluconazole as contained in BIO FLUCONAZOLE IV.
There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 to 800 mg/day) fluconazole therapy (such as BIO FLUCONAZOLE IV) for coccidioidomycosis.
A few published case reports describe a distinctive pattern of birth defects among infants whose mother received high-dose (400 to 800 mg/day) fluconazole, as contained in BIO FLUCONAZOLE IV, during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.
An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole as contained in BIO FLUCONAZOLE IV, during the first trimester.

Breastfeeding
BIO FLUCONAZOLE IV should not be given to breastfeeding women (see section 4.3).
Fluconazole as contained in BIO FLUCONAZOLE IV is distributed into the breast milk at concentrations similar to those in plasma.

4.7 Effects on the ability to drive and use machines
When driving vehicles or operating machines, it should be taken into account that dizziness or seizures may occur.

4.8 Undesirable effects
Summary of the safety profile
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 BIO FLUCONAZOLE IV.
Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section 4.4).

Tabulated list of adverse reactions

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Less frequent	Anaemia, agranulocytosis, leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity (fever and chills, skin rash or itching), anaphylaxis including angioedema, face oedema, pruritus, flushing
Metabolism and nutrition disorders	Less frequent	Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia
Psychiatric disorders	Less frequent	Somnolence, insomnia
Nervous system disorders	Frequent	Headache
	Less frequent	Seizures, nervousness, paraesthesia, dizziness, hyperkinesia, taste perversion, tremor
Eye disorders	Less frequent	Abnormal vision
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Torsades de pointes*, QT prolongation*
Gastrointestinal disorders	Frequent	Abdominal pain, vomiting, diarrhoea, nausea, loss of appetite
	Less frequent	Constipation, dyspepsia, flatulence, dry mouth, thirst
Hepatobiliary disorders	Frequent	Alanine aminotransferase (ALT) increased*, aspartate aminotransferase (AST) increased*, blood alkaline phosphatase increased*
	Less frequent	Cholestasis*, jaundice*, bilirubin increased*, hepatic toxicity including fatal cases, hepatic failure*, hepatocellular necrosis*, hepatitis*, hepato cellular damage*
Skin and subcutaneous tissue disorders	Frequent	Rash
	Less frequent	Pruritus, urticaria*, increased sweating, drug eruption (including fixed drug eruption)*, toxic epidermal necrolysis*, Stevens-Johnson syndrome*, acute generalised exanthematous-pustulosis*, exfoliative dermatitis, angioedema, face oedema, dry skin, abnormal odour, alopecia
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Less frequent	Myalgia, hypertonia
Renal and urinary disorders	Less frequent	Polyuria, female sexual dysfunction, intermenstrual bleeding, menorrhagia, leucorrhoea
General disorders and administration site conditions	Less frequent	Fatigue, malaise, asthenia, fever, rigors

* See section 4.4.

Paediatric population
The pattern and incidence of adverse events and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen 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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Symptoms
The following have been reported with an overdose of BIO FLUCONAZOLE IV: Insomnia, irritability, vomiting, diarrhoea, abdominal pains/cramps, anorexia, bulging fontanel, elevation of alkaline phosphates and gamma glutamyl transpeptidases, increase in serum calcium, renal failure, fatigue, facial rash, skin erythema, generalised urticaria, arthralgia, itching, numbness of the tongue and depressed mood. Hallucinations and paranoid behaviour have been concomitantly reported.
Treatment
Treatment is symptomatic and supportive. There is no specific antidote.
BIO FLUCONAZOLE IV is largely excreted in the urine. Forced diuresis may increase the elimination rate.
Elimination of BIO FLUCONAZOLE IV can be facilitated by haemodialysis. The concentration of BIO FLUCONAZOLE IV can be decreased by about 50 % by a three hour haemodialysis session.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A 20.2.2 Fungicides.
Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01

Mechanism of action
Fluconazole is a triazole antifungal agent. Fluconazole exerts its antifungal effect by inhibition of sterol 14-alpha-demethylase impairing the biosynthesis of ergosterol, the principal sterol in the fungal cell membrane. This damage the cell membrane, producing alterations in membrane function and permeability.
Fluconazole is specific for fungal cytochrome P-450 dependant enzymes. Fluconazole has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age.

Mechanism of resistance
There have been reports of superinfection with Candida species other than *C. albicans*, which often have inherently reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g., *C. krusei, C. auris*). Such infections may require alternative antifungal therapy.

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

Absorption
After oral administration in adults, fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90 % of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0,5 and 1,5 hours post dose. Plasma concentrations are proportional to dose. 90 % steady state levels are reached by day 4 5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90 % steady state levels by day 2.

Distribution
The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11 - 12 %).
Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80 % the corresponding plasma levels.
High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5,8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23,4 µg/g and 7 days after the second dose was still 7,1 µg/g.
Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4,05 µg/g in healthy and 1,8 µg/g in diseased nails; fluconazole was still measurable in nail samples 6 months after the end of therapy.

Elimination
Plasma elimination half-life for fluconazole is approximately 30 hours and is increased in patients with impaired renal function. The major route of excretion is renal with approximately 80 % of the administered dose appearing in the urine as unchanged medicine. A small amount of fluconazole undergoes hepatic metabolism. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites, but accumulation is significant over 15 days and concentrations may rise 2 - 3 fold.
The long plasma elimination half-life (approximately 30 hours) provides the basis for once daily dosing in the treatment of systemic conditions and single dose therapy for vaginal candidiasis and once-weekly dosing for other indications.
A pharmacokinetic study in 10 lactating women, who had temporarily or permanently stopped breastfeeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98 % of those in maternal plasma. The mean peak breast milk concentration was 2,61 mg/L at 5,2 hours post-dose.

Paediatric population
It has been reported with pharmacokinetic studies performed in children that fluconazole is cleared faster than in adults, with a half-life of 23 hours. The volume of distribution of fluconazole in children under 1 year of age (950 mL/kg) is higher than in adults (700 mL/kg). Accumulation on multiple daily dosing is therefore less and steady state plasma levels are achieved faster than in adults.
In neonates, the half-lives determined over the first 2 weeks of life are considerably longer than adult values with a mean of 74 hours at day 1 and 47 hours at day 13 of life. The volume of distribution is about 1 200 mL/kg in neonates.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Water for injection

6.2 Incompatibilities
BIO FLUCONAZOLE IV must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 30 °C.
Do not freeze.
Discard remaining contents after use.

6.5 Nature and contents of the container
BIO FLUCONAZOLE IV is packed in a 100 mL transparent white LDPE bottle. Each bottle is wrapped with a transparent clear polypropylene wrapper.

6.6 Special precautions for disposal and other handling
BIO FLUCONAZOLE IV infusion is compatible with the following administration fluids:
- Dextrose 20 %
- Ringer's solution
- Normal saline
- Potassium chloride in dextrose
- Sodium bicarbonate 4,2 %

Although no specific incompatibilities have been noted, mixing with any other medicine prior to infusion is not recommended.
BIO FLUCONAZOLE IV should be inspected visually for particles and discoloration prior to administration. The solution should only be used if it is clear and free from particles.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
BIOTECH LABORATORIES (PTY) LTD.
Ground Floor, Block K West, Central Park
400, 16th Road, Halfway House
Midrand
1685

8. REGISTRATION NUMBER
42/20.2.2/0683

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION
09 October 2009

10. DATE OF THE REVISION OF THE TEXT
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Botswana: Reg. No. BOT2003613	S2