SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Fluconazole 2 mg/mL B Braun (solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

Each mL contains 2 mg of fluconazole.

Excipient with known effect:

Each mL also contains 0,15 mmol (3,5 mg) of sodium

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless aqueous solution

pH: 4,0 – 8,0

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 B Braun is indicated for the treatment of the following conditions in adults and children:

1. Cryptococcal meningitis in mentally alert patients without localising neurological signs and as a follow up therapy after Amphotericin B therapy.
2. Maintenance therapy to prevent relapse of cryptococcal disease in patients with acquired immunodeficiency syndrome (AIDs)
3. Systemic candidiasis
4. Oropharyngeal and oesophageal candidiasis
5. Prevention of fungal infection 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

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:

For 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 received a full course of primary therapy, **Fluconazole B Braun** 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.

For 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.

For 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 receives a full course of primary therapy, **Fluconazole B Braun** may be administered at a 150 mg once weekly dose.

For 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.

The recommended **Fluconazole B Braun** dosage for the prevention of candidiasis is 50 mg to 400 mg once daily, based on the patients' 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 B Braun** 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.

Use 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 patients with impaired renal function:

Fluconazole is cleared primarily by renal excretion as unchanged drug.

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 to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

DOSAGE AND ADMINISTRATION	
Fluconazole B Braun	
Creatinine clearance (ml/min)	**Percent of recommended dose**
> 50	100 %
≤ 50	50 %
Regular haemodialysis	100 % after each dialysis

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:

[140 – age] x Wt (kg) x constant / S_{cr} (mmol/l)

Constant = 1,23 for males

Females:

[140 – age] x Wt (kg) x constant / S_{cr} (mmol/l)

Constant = 1,04 for females (0,85 x 1,23 = 1,04)

S_{cr} = serum creatinine

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.

Use 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 B Braun** is administered as a single daily dose.

1. The recommended dosage of **Fluconazole B Braun** 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 B Braun** 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 who are 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 patients with impaired renal function). 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.

Use in children 4 weeks of age and younger:

Neonates excrete fluconazole 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

Fluconazole B Braun is for intravenous infusion.

Fluconazole B Braun is formulated in 0,9 % sodium chloride solution, each 200 mg (100 mL bottle) containing 15 mmol each of Na+ and Cl-. Because **Fluconazole B Braun** is available as a dilute saline solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

Fluconazole B Braun may be infused at a maximum rate of approximately 200 mg/hour through an existing line with one of the listed fluids in section 6.6. Although no specific incompatibilities have been noted, mixing with any other medicine prior to infusion is not recommended.

For instructions on the handling of **Fluconazole B Braun** before administration, see section 6.6.

4.3. Contraindications

Hypersensitivity to the fluconazole, to related azole substances, or to any of the excipients of **Fluconazole B Braun** listed in section 6.1.

Co-administration of terfenadine is contraindicated in patients receiving **Fluconazole B Braun** at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study.

Co-administration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4, such as cisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving **Fluconazole B Braun** (see section 4.5).

Pregnancy and lactation.

4.4. Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Tinea capitis

Fluconazole as in **Fluconazole B Braun** has been studied for treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20 %.

Therefore, **Fluconazole B Braun** should not be used for *tinea capitis*.

Cryptococcosis

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

Deep endemic mycoses

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

Renal system

Fluconazole B Braun should be administered with caution to patients with renal dysfunction (see section 4.2).

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also, although less frequently seen, be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with prednisone is described in the section 4.5, 'The effects of fluconazole on other medicinal products'.

Hepatobiliary system

Fluconazole B Braun should be administered with caution to patients with liver dysfunction. Fluconazole as in **Fluconazole B Braun** has been associated with cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Hepatotoxicity may be reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during **Fluconazole B Braun** therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effects (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment with **Fluconazole B Braun** should be immediately discontinued and the patient should consult a medical practitioner.

Cardiovascular system

Some azoles, including fluconazole as in **Fluconazole B Braun**, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance there have been cases of QT prolongation and *torsades de pointes* in patients taking fluconazole as in **Fluconazole B Braun**. These reports included seriously ill patients with multiple confounding risk factors such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory.

Fluconazole B Braun should be administered with caution in patients with these potentially pro-dysrhythmic conditions.

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

Halofantrine

Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of **Fluconazole B Braun** and halofantrine is therefore not recommended (see section 4.5).

Dermatological reactions

Patients have less frequently developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis during treatment with fluconazole as in **Fluconazole B Braun**. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal

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

Hypersensitivity

Anaphylaxis has been reported (see section 4.3).

Candidiasis

Studies have shown an increasing prevalence of infections with *Candida* species other than *C. albicans*. These are often inherently resistant (e.g. *C. krusei* and *C. auris*) or show reduced susceptibility to fluconazole (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various *Candida* species to fluconazole.

Cytochrome P450

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor.

Fluconazole is also an inhibitor of CYP2C19. **Fluconazole B Braun** treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).

Terfenadine

The co-administration of **Fluconazole B Braun** at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

Excipients

This medicinal product contains 3,54 mg sodium per ml of solution. An infusion bottle containing 50 mL, 100 mL or 200 mL of solution contains 177 mg, 354 mg or 709 mg of sodium respectively,

equivalent to 8,9 %, 17,7 % or 35,5 % respectively 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

Concomitant use of the following other medicinal products is contraindicated:

Cisapride:

There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole as in **Fluconazole B Braun** and cisapride were co-administered. It was reported in a controlled study that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day, yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with **Fluconazole B Braun** and cisapride is contraindicated (see section 4.3).

Terfenadine:

Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole anti-fungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation of the QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine- is contraindicated (-see section 4.3). The co-administration of fluconazole at doses lower than 400 mg per day with terfenadine, should be carefully monitored.

Astemizole (CYP3A4 substrate):

Concomitant administration of fluconazole as in **Fluconazole B Braun** with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT

prolongation and rare occurrences of *torsades de pointes*. Co-administration of **Fluconazole B Braun** and astemizole is contraindicated (see section 4.3).

Pimozide:

Although not studied in vitro or in vivo, concomitant administration of fluconazole as in **Fluconazole B Braun** with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsade de pointes*.

Co-administration of **Fluconazole B Braun** and pimozide is contraindicated (see section 4.3).

Quinidine:

Although not studied in vitro or in vivo, concomitant administration of fluconazole as in **Fluconazole B Braun** with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Co-administration of **Fluconazole B Braun** and quinidine is contraindicated (see section 4.3).

Erythromycin:

Concomitant use of fluconazole as in **Fluconazole B Braun** 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 **Fluconazole B Braun** and erythromycin is contraindicated (see section 4.3).

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

Halofantrine:

Fluconazole as in **Fluconazole B Braun** can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of **Fluconazole B Braun** and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

Amiodarone:

Concomitant administration of fluconazole as in **Fluconazole B Braun** with amiodarone may increase QT prolongation. Therefore, caution should be taken when both medicinal products are combined, notably with high dose fluconazole (800 mg).

Concomitant use of the following other medicinal products lead to precautions and dose adjustments:

The effect of other medicinal products on fluconazole

Hydrochlorothiazide:

It was reported that in a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole as in **Fluconazole B Braun** increased plasma concentration of fluconazole by 40 %. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.

Rifampicin:

It was reported that concomitant administration of fluconazole as in **Fluconazole B Braun** 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 **Fluconazole B Braun** dose should be considered.

The effects of fluconazole on other medicinal products

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also an inhibitor of the isoenzyme CYP2C19. It was reported that in addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolised by CYP2C9, CYP2C19 and CYP3A4 co-

administered with fluconazole as in **Fluconazole B Braun**. 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 B Braun** treatment 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 in **Fluconazole B Braun**. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline:

Fluconazole as in **Fluconazole B Braun** 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. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericin B:

It was reported that concurrent administration of fluconazole as in **Fluconazole B Braun** and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants:

It was reported that in an interaction study, fluconazole as in **Fluconazole B Braun** increased the prothrombin time/international normalised ratio (INR) (12 %) after warfarin administration in healthy males.

In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melena) have been reported, in association with increases

in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

Benzodiazepines (short-acting, i.e. midazolam, triazolam):

Following oral administration of midazolam, fluconazole as in

Fluconazole B Braun resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration than with fluconazole administered intravenously. Concomitant intake of fluconazole 200 mg and midazolam 7,5 mg orally increased the midazolam AUC and half-life 3,7- fold and 2,2-fold, respectively.

Fluconazole as in **Fluconazole B Braun** increases the AUC of triazolam (single dose) by approximately 50 %, C_{max} with 20 – 32 % and increases t½ by 25 – 50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine:

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

Calcium channel blockers:

Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. Fluconazole as in **Fluconazole B Braun** has the potential to increase the systemic exposure to the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Celecoxib:

It was reported that during concomitant treatment with fluconazole as in **Fluconazole B Braun** (200 mg daily) 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 **Fluconazole B Braun**.

Cyclophosphamide:

Combination therapy with cyclophosphamide and fluconazole as in **Fluconazole B Braun** results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl:

One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was reported that in a randomised crossover study with twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly.

Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustments of fentanyl may be necessary.

HMG-CoA reductase inhibitors:

The risk of myopathy and rhabdomyolysis increases when fluconazole as in **Fluconazole B Braun** is co-administered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If

concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus, tacrolimus):

Ciclosporin:

Fluconazole as in **Fluconazole B Braun** significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2,7 mg/kg/day) there was a 1,8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus:

Although not studied in vivo or in vitro, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Sirolimus:

Fluconazole as in **Fluconazole B Braun** 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.

Tacrolimus:

Fluconazole as in **Fluconazole B Braun** may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Losartan:

Fluconazole as in **Fluconazole B Braun** inhibits the metabolism of losartan to its active metabolite (E3174), 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 in **Fluconazole B Braun** may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs:

It was reported that the C_{max} and AUC of flurbiprofen was increased by 23 % and 81 %, respectively, when co-administered with fluconazole as in **Fluconazole B Braun** 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 as in **Fluconazole B Braun** was co-administered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole as in **Fluconazole B Braun** has the potential to increase the systemic exposure of other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin:

Fluconazole as in **Fluconazole B Braun** inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC_{24} by 75 % and C_{min} by 128 %. With co-administration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone:

There was a case reported that a liver transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole as in **Fluconazole B Braun** was discontinued. The discontinuation of fluconazole as in **Fluconazole B Braun** presumably caused an enhanced CYP3A4 activity, which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin:

Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80 %. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration. Patients receiving rifabutin and **Fluconazole B Braun** concomitantly should be carefully monitored.

Saquinavir:

Fluconazole as in **Fluconazole B Braun** increases the AUC and C_{max} of saquinavir by approximately 50 % and 55 %, respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

Sulfonylureas:

Fluconazole as in **Fluconazole B Braun** 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.

Theophylline:

In a placebo-controlled interaction study, the administration of fluconazole as in **Fluconazole B Braun** 200 mg for 14 days resulted in an 18 % decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving **Fluconazole B Braun**. Therapy should be modified if signs of toxicity develop.

Vinca alkaloids:

Although not studied, fluconazole as in **Fluconazole B Braun** 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-retinoic acid (an acid form of vitamin A) and fluconazole as in **Fluconazole B Braun**, CNS related undesirable effects have developed in the form of *pseudotumor cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)**:**

Co-administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2,5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57 % (90 % CI: 20 %, 107 %) and 79 % (90 % CI: 40 %, 128 %), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine:

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

Oral contraceptives:

It was reported that two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole as in **Fluconazole B Braun**. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased by 40 % and 24 %, respectively. Thus, multiple dose use of fluconazole as in **Fluconazole B Braun** at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Endogenous steroid:

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

Ivacaftor:

Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no adequate and well-controlled studies which assessed the safety of **Fluconazole B Braun** treatment in pregnant women.

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

Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤ 450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1,29 (95 % CI 1,05 to 1,58) for 150 mg oral fluconazole and 1,98 (95 % CI 1,23 to 3,17) for doses over 450 mg fluconazole.

A few published case reports describe a distinctive and a rare pattern of birth defects among infants whose mother received high-dose (400 – 800 mg/day) fluconazole, as in **Fluconazole B Braun**, during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephalia, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.
Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom **Fluconazole B Braun** may be used if the anticipated benefit outweighs the possible risk to the foetus.

Breastfeeding

Fluconazole B Braun is found in breast milk at concentrations similar to plasma.

Fluconazole B Braun should not be used in mothers breastfeeding their infants.

Fertility

Fluconazole did not affect the fertility of male and female rats (see section 5.3).

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 taking **Fluconazole B Braun** and should be advised not to drive or operate machines until they know how treatment with **Fluconazole B Braun** affects them.

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 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 summary of adverse reactions

System Organ Class:

Blood and lymphatic system disorders:

Less frequent

Anaemia, agranulocytosis, leukopenia, neutropenia, thrombocytopenia

Immune system disorders:

Less frequent

Anaphylaxis

Endocrine disorders:

Frequency unknown

Adrenal insufficiency

Metabolism and nutrition disorders:

Less frequent

Decreased appetite, hypercholesterolemia, hypertriglyceridemia, hypokalaemia

Psychiatric disorders:

Less frequent

Somnolence, insomnia

Nervous system disorders:

Frequent

Headache

Less frequent

Seizures, paraesthesia, dizziness, taste perversion, tremor

Ear and labyrinth disorders:

Less frequent

Vertigo

Cardiac disorders:

Less frequent

Torsade de pointes (see section 4.4), QT prolongation (see section 4.4)

Gastrointestinal disorders:

Frequent

Abdominal pain, vomiting, diarrhoea, nausea

Less frequent

Constipation, dyspepsia, flatulence, dry mouth

Hepato-biliary disorders:

Frequent

Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)

Less frequent

Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4), hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)

Skin and subcutaneous tissue disorders:

Frequent

Rash (see section 4.4)

Less frequent

Drug eruption (see section 4.4), urticaria (see section 4.4), pruritus,

increased sweating, toxic epidermal necrolysis (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous-pustulosis (see section 4.4), exfoliative dermatitis, angioedema, face oedema, alopecia

Frequency unknown

drug reaction with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal, and connective tissue disorders:

Less frequent

Myalgia

General disorders and administration site conditions:

Less frequent

Fatigue, malaise, asthenia, fever

Paediatric population

The pattern and incidence of adverse reactions 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. Health care 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:

There have been reports of overdose with fluconazole as in **Fluconazole B Braun** and hallucinations and paranoid behaviour.

Treatment:

In the event of overdose, symptomatic treatment (with supportive measures) may be adequate. Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase elimination rate. A 3-hour haemodialysis session decreases plasma levels by approximately 50 %.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class of Medicine

A 20.2.2 Fungicides

Pharmacotherapeutic group: antimycotics for systemic use, triazole derivatives.

ATC code: J02A C01

Mechanism of action

Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P450 enzymes than for various mammalian cytochrome P450 enzyme systems.

Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated

response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Susceptibility *in vitro*

In vitro, fluconazole displays antifungal activity against most clinically common *Candida* specie (including *C. albicans, C. parapsilosis, C. tropicalis*). *C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole.

Fluconazole also exhibits activity *in vitro* against *Cryptococcus* neoformans and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum* and *Paracoccidoides brasilensis.*

Mechanism(s) of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy in vivo and clinically.

There have been reports of superinfection with *Candida species* other than *C. albicans*, which ~~are~~ often have inherently reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g. *C. krusei, C. auris)*. Such ~~cases~~ 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 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 level 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 approx. 80 % the corresponding plasma levels.

High skin concentrations 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 in the concentration was still 5,8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23,4 µg/g and 7 days after the second dose was still 7,1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4,05 µg/g in healthy and 1,8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11 % is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isoenzymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isoenzyme CYP2C19.

Elimination

Plasma elimination half-life for fluconazole is approx. 30 h. The major route of excretion is renal, with approximately 80 % if the administered dose appearing in the urine as unchanged medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

The long plasma elimination half-life for fluconazole provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR< 20 mL/min) half-life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50 % of fluconazole is eliminated from blood.

Paediatric Population

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single dose studies, 2 multiple dose studies and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2 – 8 mg/kg fluconazole to children between ages of 9 months to 15 years, an AUC of about 38 µg x h/mL was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 mL/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-

life after a single administration of 3 mg/kg i.v. to children of 11 days – 11 months old. The distribution volume in this age group was about 950 mL/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9 – 36 hours) and mean birth weight was 0,9 kg (range 0,75 – 1,10 kg) for 12 preterm neonates of average gestation around 28 weeks.

Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44 – 185) on day 1 which decreased, with time, to a mean of 53 (range 30 – 131) on day 7 and 47 (range 27 – 68) on day 13. The area under the curve (microgram x h/mL) was 271 (range 173 – 385) on day 1 and increased with a mean of 490 (range 292 – 734) on day 7 and decreased with a mean of 360 (range 167 – 566) on day 13. The volume of distribution (mL/kg) was 1183 (range 1070 – 1470) on day 1 and increased, with time, to a mean of 1184 (range 510 – 2130) on day 7 and 1328 (range 1040 – 1680) on day 13.

Pharmacokinetics in 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 x 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. Co-administration of diuretics did not significantly alter AUC or C_{max}. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0 - 24 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 reduce renal function characteristics of this group.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened

2 years.

After first opening:

The medicinal product must be used immediately after first opening the container. See also section 6.6.

After dilution according to directions

For mixtures with the solutions mentioned under section 6.6, chemical and physical stability has been demonstrated at 25 °C over 72 hours. From a microbiological point of view, the dilutions 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.

After first opening/dilution:

For storage conditions of the diluted medicinal product solution, see section 6.3.

6.5 Nature and contents of container

Fluconazole 2 mg/ml B Braun is presented in bottles of low-density polyethylene (LDPE),

contents: 50 mL, 100 mL, 200 mL,

Pack sizes: 10, 20 or 50 bottles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Fluconazole B Braun is for single use. After use, discard bottle and any remaining contents. Do not reconnect partially used bottles. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The product should be inspected visually for particles and discoloration prior to administration. Only solutions free of particles should be used. Do not use if the bottle is damaged.

Do not connect bottles to each other. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.

Fluconazole 2 mg/mL B Braun should be administered via intravenous infusion at a rate no greater than 200 mg per hour.

Fluconazole 2 mg/mL B Braun is compatible with the following solutions:

a) Dextrose 20 % solution for infusion

b) Ringer's solution for infusion

c) Potassium chloride solution 20 mEq/l in glucose 50 mg/ml (if available)

d) Sodium bicarbonate 42 mg/ml (4,2 %) solution for infusion

e) Sodium Chloride 9 mg/ml (0,9 %) solution for infusion (Normal saline)

Fluconazole may be infused through an existing line with one of the above listed fluids. Although no specific incompatibilities have been noted, mixing with any other medicinal products prior to infusion is not recommended.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

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10. DATE OF REVISION OF THE TEXT

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