PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

HEXAL® FLUCONAZOLE 50 (capsules)

FLUCONAZOLE UNICORN 150 (capsules)

HEXAL® FLUCONAZOLE 200 (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each HEXAL FLUCONAZOLE 50 capsule contains 50 mg fluconazole.

Each FLUCONAZOLE UNICORN 150 capsule contains 150 mg fluconazole.

Each HEXAL FLUCONAZOLE 200 capsule contains 200 mg fluconazole.

Each HEXAL FLUCONAZOLE 50 capsule contains sugar (lactose monohydrate 48,75 mg).

Each FLUCONAZOLE UNICORN 150 capsule contains sugar (lactose monohydrate 146,25 mg).

Each HEXAL FLUCONAZOLE 200 capsule contains sugar (lactose monohydrate 195,0 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

HEXAL FLUCONAZOLE 50: Hard gelatin capsules, snap-fit closure, turquoise cap / white body with the imprint FC50, containing a white odourless powder.

FLUCONAZOLE UNICORN 150: Hard gelatin capsules, snap-fit closure, white cap / white body, with the imprint FC150, containing a white odourless powder.

HEXAL FLUCONAZOLE 200: Hard gelatin capsules, snap-fit closure, purple cap / white body, with the imprint FC200, containing a white odourless powder.

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.

HEXAL FLUCONAZOLE AND FLUCONAZOLE UNICORN 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.

Fluconazole 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

Cryptococcal meningitis:

***Adults*:** Initial dose is 400 mg on the first day; followed by 200 mg to 400 mg daily depending on the clinical response. Duration of therapy is based on clinical mycological response, but is usually 8 weeks, following Amphotericin B therapy and 10 weeks with HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN monotherapy.

***Children over 4 weeks of age*:** 6 mg/kg/day to 12 mg/kg/day depending on the severity of the infection.

Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with AIDS:

***Adults*:** 100 mg to 200 mg per day.

Systemic candidiasis:

***Adults*:** Initial dose is 400 mg on the first day; followed by 200 mg daily. The dose may be increased to 400 mg daily depending on the clinical response.

***Children over 4 weeks of age*:** 6 mg/kg/day to 12 mg/kg/day depending on the severity of the infection. Duration of therapy is based on clinical and mycological response.

Oropharyngeal candidiasis:

***Adults*:** 50 mg to 100 mg daily for 7 to 14 days. Severely immunocompromised patients may require longer treatment periods.

To prevent relapse in AIDS patients: 150 mg of HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN may be given once a week.

***Children over 4 weeks of age*:** Initial dose is 6 mg/kg on the first day; followed by 3 mg/kg once daily. Duration of treatment is at least 2 weeks to decrease the risk of relapse.

Oesophageal candidiasis:

***Adults*:** Initial dose is 200 mg on the first day; followed by 100 mg to 200 mg daily. Doses up to 400 mg once a day may be used if there is no clinical response after 14 days on the lower dose. Duration of treatment is at least 3 weeks and for an additional 2 weeks after symptoms have resolved.

***Children over 4 weeks of age*:** Initial dose is 6 mg/kg on the first day; followed by 3 mg/kg once daily. Dose may be increased to 12 mg/kg/day based on the condition of the patient and the response to the

medicine. Duration of treatment is for at least 3 weeks and for an additional 2 weeks after the symptoms have resolved.

Prophylaxis of fungal infections in patients who receive cytotoxic chemotherapy and/or radiation therapy:

***Adults*:** 50 mg to 400 mg daily depending on the patients risk for developing fungal infections. Treatment should be started several days before the onset of neutropenia is expected and continued for 7 days after the neutrophil count rises above 1000 cells per mm^3.

***Children over 4 weeks of age*:** 3 to 12 mg/kg/day depending on the extent and duration of the induced neutropenia.

Vaginal candidiasis:

***Adults*:** 150 mg administered as a single dose.

Recurrent vaginal candidiasis:

***Adults*:** 150 mg administered as a single dose, once a month. The duration of therapy is individualised, but ranges from 4 to 12 months.

Candida balanitis:

***Adults*:** 150 mg administered as a single dose.

Dermal infections including *tinea pedis*, *tinea corporis*, *tinea cruris*, *tinea unguium* (onychomycosis) and dermal candida infections:

***Adults*:** 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 continue until the infected nail grows out and is replaced with an uninfected nail. Fingernails generally require 3 to 6 months to regrow and toenails 6 to 12 months.

Safety and efficacy of HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN in children has not been established for the following indications:

Recurrent vaginal candidiasis, candida balanitis, dermal infections including *tinea pedis*, *tinea corporis*, *tinea cruris*, *tinea unguium* (onychomycosis) and dermal candida infections.

Elderly: (see “dosage in renal failure”).

Normal dosage recommendations are used in the elderly unless the patient has decreased renal function, in which case an adjustment in dosage or dosing interval is required.

Dosage in renal failure:

HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN should be used with caution in patients with renal function impairment. HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN is excreted through the kidneys.

A dosage reduction or increase in dosing interval is recommended:

1. The normal loading dose or the initial dose should be given on the first day of treatment.
2. Subsequent doses should be adjusted according to the creatinine clearance.

If creatinine clearance is > 50 ml/min the normal dose can be given.

If creatinine clearance is < 50 ml/min and patient is not receiving dialysis, 50 % of the normal dose can be given.

Patients on regular haemodialysis should receive a standard dose of HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN after each dialysis session.

The patient’s creatinine clearance (Cl_{cr}) can be estimated by using the following formula:

$$\mathbf{eCl_{cr}} = \frac{\mathbf{[140 - age] \times Wt\ (Kg) \times 0{,}85\ (if\ female)}}{\mathbf{S_{cr}\ (\mu mol/L)}}$$

The pharmacokinetics of HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN has not been studied in children with impaired renal function. Recommendations for dosage reduction in such children should parallel the recommendations for adults.

- The dose of HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN and the duration of treatment should be based on the site of infection and the individual's response to therapy.
- Treatment should be continued until clinical parameters and laboratory tests indicate that active fungal infection has subsided.
- AIDS patients with cryptococcal meningitis or recurrent oropharyngeal candidiasis require maintenance therapy to prevent relapse.
- For infants under 2 weeks of age, the above children's doses should be used, but only given once every 72 hours. For those aged between 2 and 4 weeks the dose should be given every 48 hours. The maximum adult daily dose (i.e. 400 mg) should not be exceeded in children.
- Normal dosage recommendations are used in the elderly population, unless the patient has decreased renal function, in which case an adjustment in dosage or dosing interval is required.

4.3 Contraindications

- Hypersensitivity to HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN, other azole antifungal medicines, or to any of the excipients.
- Co-administration of terfenadine in patients receiving multiple doses of HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN in doses of 400 mg per day or greater (see section 4.5).
- Co-administration of cisapride (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Multiple dose therapy is contraindicated in patients with renal impairment.
- Concurrent use with astemizole should be avoided.

4.4 Special warnings and precautions for use

Tinea capitis:

Fluconazole has been studied for treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20 %. Therefore, HEXAL FLUCONAZOLE / FLUCONAZOLE UNICORN should not be used for *tinea capitis.*

Cryptococcosis:

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

Deep endemic mycoses:

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

Renal system:

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

Adrenal insufficiency:

Ketoconazole is known to cause adrenal insufficiency, and this could also, although rarely seen, be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with prednisone, see section 4.5 'The effect of fluconazole on other medicines'.

Hepatobiliary system:

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

Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities related to dose and duration of use, primarily in patients with serious underlying medical conditions. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Liver function should be monitored periodically in all patients receiving continuous treatment with fluconazole for more than one month. Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a doctor if these symptoms are experienced.

Underlying diseases:

Fluconazole should be used with caution in patients with underlying disease, such as AIDS or malignancy. Abnormalities in haematological, hepatic and renal function have been observed.

Cardiovascular system:

Some azoles, including fluconazole, 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 very rare cases of QT prolongation and *torsades de pointes* in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory. Patients with hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and *torsades de pointes*.

Fluconazole should be administered with caution to patients with potentially proarrhythmic 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 fluconazole and halofantrine is therefore not recommended (see section 4.5).

Dermatological reactions:

Patients have less frequently developed pruritus, rashes, urticaria, angioedema, dry skin, abnormal odour, exfoliative cutaneous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis during treatment with fluconazole. AIDS patients are more prone to the development of

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

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported.

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.

Hypersensitivity:

In rare cases anaphylaxis has been reported (see section 4.3).

Cytochrome P450:

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

Terfenadine:

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

Lactose:

Fluconazole capsules contain lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take fluconazole.

Fluconazole capsules contain lactose monohydrate, which may have an effect on the glycaemic control of patients with diabetes mellitus.

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 and cisapride were co-administered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

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

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

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

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

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

Concomitant use of the following other medicines cannot be recommended:

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

Concomitant use that should be used with caution:

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

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

The effect of other medicines on fluconazole:

Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25 % decrease in the AUC and a 20 % shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.

Interaction studies have shown that when oral fluconazole is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

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

The effect of fluconazole on other medicines:

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 3A4 and 2C9. 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 concentrations of the 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 to 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC_{10} increased 2-fold, probably through inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and

antagonism of the two medicines in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, 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 resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7,5 mg orally increased the midazolam AUC and half-life 3,7-fold and 2,2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0,25 mg orally increased the triazolam AUC and half-life 4,4-fold and 2,3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If 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 inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30 % has been observed. There is a risk of developing carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

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

Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg) the celecoxib C_{max} and AUC increased by 68 % and 134 %, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

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

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is 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 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 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 and erythromycin.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.

Immunosuppresors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):
Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2,7 mg/kg/day) there was a 1,8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

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

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

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

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74), which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Nevirapine: 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 fluconazole are given concomitantly and patients should be monitored closely.

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 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.

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

Rifabutin: Fluconazole increases serum concentrations of rifabutin leading to increase in the AUC of rifabutin of 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.

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

Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. 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 200 mg for 14 days resulted in an 18 % decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

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

Tolvaptan: Tolvaptan exposure increases significantly (AUC by 200 %, C_{max} by 80 %) with concomitant use of tolvaptan, a CYP3A4 substrate, with fluconazole, a moderate CYP3A4 inhibitor. This results in a significantly increased risk of undesirable effects, especially diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced as described in

the tolvaptan summary of product characteristics and the patient should be monitored regularly for undesirable effects associated with tolvaptan.

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9, 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 of voriconazole by an average of 57 % (90 % CI: 20 %,
107 %) and 79 % (90 % CI: 40 %, 128 %), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases 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.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg

oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

Oral contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40 % and 24 %, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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

There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400 - 800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole should not be used in pregnancy (see section 4.3).

Breastfeeding:

Fluconazole should not be given to breastfeeding women (see section 4.3). Fluconazole passes into breast milk to reach concentrations similar to those in plasma (see section 5.2).

Fertility:

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

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of fluconazole on the ability to drive or use machines.

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

4.8 Undesirable effects

Blood and lymphatic system disorders:

***Less frequent*:** Anaemia, leucopenia, neutropenia, agranulocytosis and thrombocytopenia.

Immune system disorders:

***Less frequent*:** Anaphylaxis.

Metabolism and nutrition disorders:

***Less frequent*:** Decreased appetite, hypokalaemia, hypercholesterolaemia, hypertriglyceridaemia.

Psychiatric disorders:

***Less frequent*:** Somnolence, insomnia.

Nervous system disorders:

***Frequent*:** Headache.

***Less frequent*:** Dizziness, seizures, paraesthesia, taste perversion, tremor.

Ear and labyrinth disorders:

***Less frequent*:** Vertigo.

Cardiac disorders:

***Less frequent*:** QT-prolongation, torsade de pointes (see section 4.4).

Gastrointestinal disorders:

***Frequent*:** Nausea, vomiting, abdominal pain, diarrhoea.

***Less frequent*:** Constipation, dyspepsia, dry mouth, flatulence.

Hepatobiliary disorders:

***Frequent*:** Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased (see section 4.4).

***Less frequent*:** Hepatic failure, hepatitis, hepatocellular necrosis, hepatocellular damage, jaundice, bilirubin increased, cholestasis (see section 4.4).

Skin and subcutaneous tissue disorders:

***Frequent*:** Rash (see section 4.4).

***Less Frequent*:** Drug eruption* (see section 4.4), alopecia, urticaria (see section 4.4), pruritus, increased sweating, dermatitis exfoliative, Stevens-Johnson syndrome (see section 4.4), toxic epidermal necrolysis (see section 4.4), acute generalised exanthematous pustulosis (see section 4.4), angioedema, face oedema.

Frequency unknown: Drug reaction with eosinophilia and systemic symptoms (DRESS).

* including Fixed drug eruption

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 undesirable effects and laboratory abnormalities recorded during paediatric clinical trials with fluconazole, excluding the genital candidiasis indication, are comparable to those seen in adults.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the 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 product Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Suspected side effects can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

The following have been reported with an overdose of fluconazole:

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. Hallucination and paranoid behaviour have been concomitantly reported.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemodialysis session decreases plasma levels of fluconazole by approximately 50 %.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.2.2 Antimicrobial (chemotherapeutic) agents. Fungicides

5.1 Pharmacodynamic properties

Mechanism of action:

Fluconazole is a triazole antifungal medicine. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole.

Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Fluconazole 50 mg daily given up to 28 days has 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* species (including *C. albicans, C. parapsilosis, C. tropicalis). C. glabrata* shows a wide range of susceptibility while *C. krusei* is 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 *Paracoccidioides brasiliensis*.

Pharmacokinetic / pharmacodynamic relationship:

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly, cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanisms of resistance:

Candida spp have developed a number of resistance mechanisms to azole antifungal medicines. 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 inherently not susceptible to fluconazole (e.g. *Candida krusei*). Such cases 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 or gastric acidity. Peak plasma concentrations in the fasting state occur between 1 to 2 hours post-dose. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4 to 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 to 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; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation:

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

Elimination:

Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80 % of the administered dose appearing in the urine as unchanged medicine. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites. However, accumulation is significant over 15 days and concentrations may rise 2 to 3 fold. A small amount of fluconazole undergoes hepatic metabolism. The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.

Pharmacokinetics in renal impairment:

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

Pharmacokinetics during lactation:

A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped 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. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0,39 mg/kg/day, which is approximately 40 % of the recommended neonatal dose (< 2 weeks of age) or 13 % of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children:

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

After administration of 2 – 8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life 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 new-borns. The mean age at first dose was 24 hours (range 9 – 36 hours) and mean birth weight was 0,9 kg (range 0,75 – 1,10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44 – 185) on day 1 which decreased, with time to a mean of 53 (range 30 – 131) on day 7 and 47 (range 27 – 68) on day 13. The area under the curve (µg.h/ml) was 271 (range 173 – 385) on day 1 and increased with a mean of 490 (range 292 – 734) on day 7 and decreased with a mean of 360 (range 167 – 566) on day 13. The

volume of distribution (ml/kg) was 1183 (range 1070 – 1470) on day 1 and increased, with time, to a mean of 1184 (range 510 – 2130) on day 7 and 1328 (range 1040 – 1680) on day 13.

Pharmacokinetics in elderly:

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1,54 µg/ml and occurred at 1,3 hours post-dose. The mean AUC was 76,4 ± 20,3 µg·h/ml, and the mean terminal half-life was 46,2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Co-administration of diuretics did not significantly alter AUC or C_{max}. In addition, creatinine clearance (74 ml/min), the percent of medicines recovered unchanged in urine (0 – 4 h, 22 %) and the fluconazole renal clearance estimates (0,124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

5.3 Preclinical safety data

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

Carcinogenesis:

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2,5, 5, or 10 mg/kg/day (approximately 2 – 7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Mutagenesis:

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *Salmonella typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 µg/ml) showed no evidence of chromosomal mutations.

Reproductive toxicity:

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal silica, hard gelatin capsule*****, lactose monohydrate, magnesium stearate, maize starch, sodium lauryl sulfate.

****Hard Gelatin capsule composed of:***

Gelatin, indigo carmine FD&C Blue 2**, Ponceau 4 R***, titanium dioxide.

***available in HEXAL FLUCONAZOLE 50 and HEXAL FLUCONAZOLE 200 only*

****available in HEXAL FLUCONAZOLE 200 only.*

Imprinting ink (all capsules):

Black iron oxide (E 172), propylene glycol (E 1520), shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Do not remove the blisters from the outer container until required for use.

6.5 Nature and contents of container

HEXAL FLUCONAZOLE 50: White, opaque PVC/Aluminium blister strips containing 14 capsules.

FLUCONAZOLE UNICORN 150: White, opaque PVC/Aluminium blister strips containing 1 or 4 capsules.

HEXAL FLUCONAZOLE 200: White, opaque PVC/Aluminium blister strips containing 28 or 30 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1], Waterfall 5-Ir, Magwa Crescent West, Waterfall City, Jukskei View, 2090.

Marketed by: Unicorn Pharmaceuticals (Pty) Ltd.

8. REGISTRATION NUMBER(S)

HEXAL FLUCONAZOLE 50: 36/20.2.2/0264

FLUCONAZOLE UNICORN 150: 36/20.2.2/0265

HEXAL FLUCONAZOLE 200: 36/20.2.2/0266

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

06 June 2003

10. DATE OF REVISION OF THE TEXT

16 July 2021

[1]Company Reg. No.: 1990/001979/07