**Summary of Product Characterization**

**1. Name of the medicinal product**
AUSTFLUZOL (Fluconazole Tablets 150 mg)

**2. Qualitative and Quantitative Composition**
Each uncoated tablet contains:
Fluconazole USP 150 mg
Colour: Ponceau 4R

**3. Pharmaceutical form**
Oral uncoated tablet
The 150 mg uncoated tablet has a pink color, round, flat, beveled edge, uncoated tablet having breakline on one side and plain on other side.

**4. Clinical particulars**

**4.1 Therapeutic indications**

Austfluzol is indicated for the treatment of the following conditions:-

• Vaginal candidiasis, acute or recurrent; or candidal balanitis associated with vaginal candidiasis.

• Dermatomycosis including *tinea pedis, tinea corporis, tinea cruris, tinea versicolor* and dermal *candida* infections when systemic therapy is indicated.

• *Tinea unguinium (onychomycosis)* when other agents are not considered appropriate.

- Coccidioidomycosis
- Cryptococcal meningitis

**4.2 Posology and method of administration**

The daily dose of AUSTFLUZOL should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. 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.

**Adults**

1. ***(a). Cryptococcal meningitis*** and ***cryptococcal infections at other sites***: The usual dose is 400 mg on the first day followed by 200 to 400 mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6-8 weeks for cryptococcal meningitis.

***(b). Prevention of relapse of cryptococcal meningitis in AIDS patients:*** After the patient receives a full course of primary therapy, AUSTFLUZOL may be administered indefinitely at a once daily dose of 200 mg.

2. ***Candidaemia, disseminated candidiasis and other invasive candidal infections:*** The usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response, the dose may be increased to 400 mg once daily. Duration of treatment is based upon the clinical response.
3. ***Oropharyngeal candidiasis:*** The usual dose is 50 mg once daily for 7-14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function. For atrophic oral candidiasis associated with dentures the usual dose is 50 mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.

   For other candidal infections of mucosa (except vaginal candidiasis, see below), e.g. oesophagitis, candiduria, mucocutaneous candidiasis etc., the usual effective dose is 50 mg once daily, given for 14-30 days.

   In unusually difficult cases of mucosal candidal infections the dose may be increased to 100 mg daily.
4. ***Vaginal candidiasis:*** AUSTFLUZOL should be administered as a single oral dose.

   Median time to onset of symptom relief following a 150 mg single oral dose for the treatment of vaginal candidiasis is one day. The range of time to onset of symptom relief is one hour to nine days.

5. ***Prevention of fungal infections in immunocompromised patients:*** The dose should be 50 mg once daily while the patient is at risk as a consequence of receiving cytotoxic chemotherapy, radiotherapy or bone marrow transplant. A higher dose of 100 mg/day may be used in patients at risk of severe recurrent infections.

6. ***Dermatomycoses:*** The usual dosage is 50 mg once daily or 150mg once weekly for two to four weeks. Tinea pedis may require treatment for up to six weeks.

**Children**

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. AUSTFLUZOL is administered as a single dose each day.

1. ***Mucosal candidiasis:*** 3 mg/kg once daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady state levels more rapidly.
2. ***Systemic candidiasis and cryptococcal infection:*** 6-12 mg/kg once daily, depending on the severity of the disease.

3. ***Prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy:*** 3 - 12 mg/kg once daily, depending on the extent and duration of the induced neutropenia (see adult dosing).

For children with impaired renal function the daily dose should be reduced in accordance with the guidelines given for adults.

**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.

**Elderly**

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

**Renal Impairment**

Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single dose therapy are necessary.

In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50 mg to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

| **Creatinine Clearance (mL/min)** | **Percent of Recommended Dose** |
|---|---|
| > 50 | 100 % |
| 11 – 50 | 50 % |
| Patients receiving haemodialysis | One dose after every haemodialysis session |

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of patient) should be used to estimate the creatinine clearance in mL/minute:

Males:

$$\frac{\textbf{Weight (kg) x (140 – age) x 0.0885}}{\textbf{72 x serum creatinine (mmol/L)}}$$

Females:

**0.85 x above value**

Method of administration

For oral use

**4.3 Contraindications**

AUSTFLUZOL should not be used in patients with known sensitivity to fluconazole; to related azole compounds; or to any of its excipients.

Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg/day or higher based upon results of a multiple dose interaction study. Co-administration of other drugs known to prolong the QT interval and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine is contraindicated in patients receiving fluconazole .

**4.4 Special warnings and special precautions for use**

Anaphylaxis has been reported in rare instances.

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

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

Patients who develop abnormal liver function tests during AUSTFLUZOL therapy should be monitored for the development of more severe hepatic injury. AUSTFLUZOL should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to fluconazole (see section 1.8.4.8).

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with AUSTFLUZOL. AIDS patients are more prone to the development of serious cutaneous reactions to many drugs. If rash which is attributable to fluconazole develops in a patient treated for a superficial fungal infection, AUSTFLUZOL should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and AUSTFLUZOL discontinued if bullous lesions or erythema multiforme develop .

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 medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. 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 these potentially proarrhythmic conditions .

In rare cases, as with other azoles, anaphylaxis has been reported.
Fluconazole should be administered with caution to patients with renal dysfunction.
Fluconazole is a moderate CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of the isoenzyme CYP2C19. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4 should be monitored.
Adrenal insufficiency has been reported in patients receiving other azoles (e.g., ketoconazole). Reversible cases of adrenal insufficiency were reported in patients receiving fluconazole.
Fluconazole has been associated with rare 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 patients has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during Fluconazole therapy should be monitored for the development of more serious hepatic injury. The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

**4.5 Interaction with other medicinal products and other forms of interaction**

**Pharmacokinetic Interactions**

Fluconazole is an inhibitor of the cytochrome P450 system, particularly the CYP 2C and to a lesser extent the CYP 3A isoforms. *In vitro* studies conducted in human hepatic microsomes, demonstrate that the extent of inhibition of CYP 3A isoforms is lowest with fluconazole, when compared with ketoconazole and itraconazole. In addition to the observed /documented interactions mentioned below, co-administration of fluconazole with other drugs metabolised primarily by these P450 isoforms may result in altered plasma concentrations of these drugs that could change therapeutic effects and/or adverse event profiles.
As fluconazole is a potent inhibitor of CYP 2C9, CYP 2C19 and moderate inhibitor of CYP 3A4, particular caution should be exercised when fluconazole is co-administered with other compounds metabolised by these isoenzymes and these 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

**Interactions between Fluconazole and Other Agents**

Clinically or potentially significant drug interactions observed between fluconazole and the following agents are described below.

***Azithromycin:*** An open-label, randomised, 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.

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

***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).

***Amitriptyline, nortriptyline*:** Fluconazole increases the effect of amitriptyline and nortriptyline. 5-Nortriptyline and/or S-amitnptyline may be measured at initiation of the combination therapy and after 1 week. Dosage 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 *Candida albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two drugs in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

***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 *torsade de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 1.8.4.3).

***Benzodiazepines (short acting):*** Studies in human subjects have reported changes in midazolam pharmacokinetics and clinical effects that are dependent on dosage and route of administration. Single doses of fluconazole 150 mg resulted in modest increases in midazolam concentrations and psychomotor effects following oral administration of 10 mg that may not be clinically significant. At doses used to treat systemic mycoses, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects following oral administration of midazolam 7.5 mg, but only modest increases that are not likely to be clinically significant following intravenous infusion of midazolam 0.05 mg/kg.

This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. There have been reports of sleepiness and disturbed consciousness in patients taking fluconazole for systemic mycoses and triazolam; however, in most of these cases the patients had serious underlying illnesses and/or concomitant therapies that could have contributed to the reported events, and a relationship to a fluconazole-triazolam interaction is uncertain. If concomitant benzodiazepine therapy is necessary in patients being treated with AUSTFLUZOL, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored. Fluconazole increases the area under the concentration versus time curve (AUC) of triazolam (single dose) by approximately 50% Cmax by 20% to 32% and increases the half life by 25% to 50% due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

***Carbamazepine:*** Azole antifungals may raise carbamazepine plasma concentrations. Since high plasma concentrations of carbamazepine and/or cabamazepine-10, 11-epoxy may result in adverse effects (e.g.: dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or plasma concentrations monitored when used concomitantly with fluconazole.

***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 Cmax and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

***Cisapride:*** There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illness. 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. Coadministration of cisapride is contraindicated in patients receiving fluconazole.

***Cyclosporin:*** Fluconazole significantly increases the concentration and AUC of cyclosporin. This combination may be used by reducing the dosage of cyclosporin depending on cyclosporin concentration.

***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.

***Erythromycin:*** Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsade de pointes) and consequently sudden heart death. This combination should be avoided.

***Fentanyl:*** One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomised crossover study with 12 healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

***Halofantrine:*** Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4.

***HMG-CoA reductase inhibitors:*** The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and 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.

***Gastrointestinal drugs:*** In fasted normal volunteers, absorption of orally administered fluconazole does not appear to be affected by agents that increase gastric pH. Single dose administration of fluconazole (100 mg) with cimetidine (400 mg) resulted in a 13% reduction in AUC and 21% reduction in Cmax of fluconazole. Administration of antacid containing aluminium and magnesium hydroxides immediately prior to a single dose of fluconazole (100 mg) had no effect on the absorption or elimination of fluconazole.

***Hydrochlorothiazide:*** Concomitant oral administration of 100 mg fluconazole and 50 mg hydrochlorothiazide for 10 days in normal volunteers resulted in an increase of 41% in Cmax and an increase of 43% in area under the concentration versus time curve (AUC) of fluconazole, compared to fluconazole given alone. Overall the plasma concentrations of fluconazole were approximately 3.26 - 6.52 μmol/L higher with concomitant diuretic. These changes are attributable to a mean net reduction of approximately 20% in renal clearance of fluconazole.

***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 that occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

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

***Non-steroidal anti-inflammatory drugs:*** Although not specifically studied, fluconazole has

the potential to increase the systemic exposure of other non-steroidal anti-inflammatory drugs (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 dosage of NSAIDs may be needed.

***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.

***Oral contraceptives:*** Three kinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on either 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. In a 300 mg once weekly fluconazole study, the AUCs of ethinyl estradiol and norethindrone were increased by 24% and 13%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

***Oral hypoglycaemic agents:*** The effects of fluconazole on the pharmacokinetics of the sulphonylurea oral hypoglycaemic agents tolbutamide, glipizide and glibenclamide were examined in three placebo-controlled crossover studies in normal volunteers. All subjects received the sulphonylurea alone and following treatment with 100 mg of fluconazole as a single daily oral dose for 7 days. Fluconazole administration resulted in significant increases in Cmax and AUC of the sulphonylurea. Several subjects in these three studies experienced symptoms consistent with hypoglycaemia. In the glibenclamide study, several volunteers required oral glucose treatment. When AUSTFLUZOL and sulphonylureas are coadministered, blood glucose concentrations should be monitored carefully and the dose of the sulphonylurea adjusted accordingly.

***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 torsade de pointes. Coadministration of fluconazole and pimozide is contraindicated.

***Phenytoin*****:** Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

***Prednisone:*** There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a 3 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.

***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 *torsade de pointes*. Coadministration of fluconazole and quinidine is contraindicated.

***Rifabutin:*** There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and AUSTFLUZOL concomitantly should be carefully monitored.

***Rifampicin:*** Administration of a single oral 200 mg dose of fluconazole after chronic rifampicin administration resulted in a 25% decrease in AUC and a 20% shorter half-life of fluconazole in normal volunteers. Depending on clinical circumstances, an increase of the dose of AUSTFLUZOL should be considered when it is administered with rifampicin.

***Saquinavir:*** Fluconazole increases the AUC of saquinavir and decreases the clearance of saquinavir due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

***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 dosage adjustment of sirolimus depending on the effect/concentration measurements.

***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 dosage are recommended during coadministration.

***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. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

***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 of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk of theophylline toxicity should be observed for signs of theophylline toxicity while receiving AUSTFLUZOL and therapy modified appropriately if signs of toxicity develop.

***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/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. The coadministration of fluconazole at doses lower than 400 mg/day with terfenadine should be carefully monitored.

***Tofacitinib:*** Exposure of tofacitinib is increased when tofacitinib is coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Dosage adjustment of tofacitinib may be necessary.

***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, central nervous system (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): Concurrent 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 6 healthy male subjects resulted in an increase in Cmax and AUC, of voriconazole by an average of 57% (90% C1: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended.

***Warfarin:*** A single dose of warfarin (15 mg) given to normal volunteers, following 14 days of orally administered fluconazole (200 mg) resulted in a 12% increase in the prothrombin time response (area under the prothrombin time-time curve). One of 13 subjects experienced a 2-fold increase in his prothrombin time response. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melaena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Careful monitoring of prothrombin time in patients receiving AUSTFLUZOL and coumarin-type or indanedione anticoagulants is recommended.

***Zidovudine:*** Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200 mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment crossover study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200 mg every eight hours either with or without fluconazole 400 mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

**4.6Fertility**, **Pregnancy and Lactation**

**Pregnancy**

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus.

Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.

There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester.

There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 mg/kg to 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Adverse foetal effects have been seen in animals only at high dose levels associated with maternal toxicity. These findings are not considered relevant to fluconazole used at therapeutic doses.

Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high-dose (400 mg/day to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

**Breast-feeding**

AUSTFLUZOL is found in human breast milk at concentrations similar to plasma. The

elimination half-life from breast milk approximates the plasma elimination half-life of 30 hours. 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.

Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for AUSTFLUZOL and any potential adverse effects on the breastfed child from AUSTFLUZOL or from the underlying maternal condition.

A pharmacokinetic study in 10 lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of Diflucan. 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.

**Fertility**

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5 mg/kg, 10 mg/kg or 20 mg/kg or with parenteral doses of 5 mg/kg, 25 mg/kg or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5 mg/kg, 20 mg/kg and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/kg. 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. The effects on parturition in rats 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.

### 4.7 Effects on ability to drive and use machines

Experience with AUSTFLUZOL indicates that therapy is likely to produce minor or moderate adverse effects on the ability to drive or use machinery. When driving vehicles or operating machinery it should be taken into account that occasionally dizziness or seizures may occur.

### 4.8 Undesirable effects

**Adults**

The safety profile of fluconazole appears similar in adults and children. The profile established for adults, given different dosage regimens and for different indications, is given

below.

**1. Multiple daily dosing for treatment of oral and for oral and oropharyngeal candidiasis; cryptococcal meningitis; or systemic candidiasis.**

| | |
|---|---|
| **Common (≥1 % and <10 %)** | |
| Gastrointestinal disorders | Nausea, vomiting, abdominal pain, diarrhoea. |
| Nervous system disorders | Headache |
| **Uncommon (≥0.1 % and <1 %)** | |
| Nervous system disorder | Seizures, dizziness, paraesthesia, taste perversion |
| Skin and subcutaneous tissue disoreders | Rash |
| **Rare (≥0.01 % and <0.1 %)** | |
| Blood and lymphatic system disorders | Leukopenia (including neutropenia and agranulocytosis), thrombocytopenia |
| Immunological system disorders | Anaphylaxis, angioedema |
| Metabolism and nutrition disorders | Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia |
| Nervous system disorders | Tremors |
| Skin and subcutaneous tissue disoreders | Angioedema, exfoliative skin disoreders including Steven-Johnson syndrome and toxic epidermal necrolysis, alopecia. |

**2. Single 150 mg dose for vaginal candidiasis**

| | |
|---|---|
| **Common (≥1 % and <10 %)** | |
| Gastrointestinal disorders | Nausea, abdominal pain, diarrhoea, dyspepsia |
| Hepatobiliary disorders | Alanine aminotransferase increased, aspartate aminotranferase increased, blood alkaline phosphatase increased. |
| Nervous system disorders | Headache |
| **Uncommon (≥0.1 % and <1 %)** | |
| Eye disorders | Abnormal vision |
| Gastrointestinal disorders | Constipation, flatulence, vomiting, loose stools, dry mouth |
| General disorders and administration site conditions | Thirst, fatigue, malaise, pain, rigors, asthenia, fever |
| Infeactions and infestations | Pharyngitis, herpes simplex |
| Metabolism and nutrition disorders | Anorexia |
| Musculoskeletal and connective tisue disorders | Back pain, myalgia |
| Nervous system disorders | Dissiness, vertigo, hyperkinesia, hypertonia, taste perversion, visual field defect |
| Psychiatric disorders | Insomnia, nervousness |
| Renal and urinary disorders | Polyuria, renal pain |
| Reproductive system and breast disorders | Intermenstrual bleeding, dysmenorrhoea, leukorrhoea, menorrhagia, uterine spasm, vaginal disorder, female sexual dysfunction |
| Skin and subcutaneous tissues disoreders | Pruritus, genital pruritus, rash, erythematous rash, dry skin, abnormal skin odour, urticaria |
| Vascular disorders | Flushing, hot flushes |
| **Rare (≥0.01 % and <0.1 %)** | |
| Hepatobilliary disorders | Hepatic toxicity, including rare cases of |

| | |
|---|---|
| | fatalities. Hepatic failure, hapatocellular necrosis, hepatitis, hepatocellular damage. |
| Cardiac disorders | Torsade de pointes, QT prolongation |

**3. Patients treated with 150 mg weekly in dermal therapeutic studies**

| **Common (≥1 % and <10 %)** | |
|---|---|
| Gastrointestinal disorders | Abdominal pain, dyspepsia |
| Nervous system disorders | Headache |
| Skin and subcutaneous tissue disorders | Acne |
| **Uncommon (≥0.1 % and <1 %)** | |
| Investigations | Elevation of transaminase >2-3 x upper limit of normal |
| Nervous system disorders | Paraesthesia, somonolence |
| Phychiatric disorders | Insomnia, somonolence |
| Skin and subcutaneous tissue disorders | Pruritus, urticaria, increased sweating, drug eruption (including fixed drug eruption). |

**Children:**

| **Common (≥1 % and <10 %)** | |
|---|---|
| Gastrointestinal disorders | Vomiting, diarrhoea, abdominal pain |
| **Uncommon (≥0.1 % and <1 %)** | |
| Cardiac disorders | Cardiomyopathy |
| Ear and labyrinth disorders | Deafness |
| Gastrointestinal disorders | Nausea, dyspepsia, ileus, stomatitis, loos stools |
| Hepatobiliary disorders | Hepatocellular damage, jaundice |
| Infections and infestations | Infection |
| Metabolism and nutrition disorders | Anorexia |
| Nervous system disorders | Headache, taste perversion |
| Respiratory, thoracic and mediastinal disorders | Hypoxia, respiratory disorder |
| Skin and subcutaneous tissue disorders | Rash (erythematous & maculo-papular), pruritus, purpura |
| Vascular disorders | Hypertension |

**4.9 Overdose**

**Symptoms:** There have been reports of overdosage with fluconazole and in one reported case, a 42-year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to the hospital, and his condition resolved within 48 hours.

**Treatment:** In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Fluconazole is largely excreted in urine. A 3-hour hemodialysis session decreases plasma levels by approximately 50%.

## 5.PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamics properties

**Mechanism of Action**

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14-α-demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14-α-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

**Pharmacodynamics**

The effects of fluconazole on the metabolism of carbohydrates, lipids, adrenal and gonadal hormones were assessed. In normal volunteers, fluconazole administration at doses ranging from 200 to 400 mg once daily for up to 14 days was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the adrenocorticotropic hormone (ACTH) stimulated cortisol response. In addition, fluconazole appears to have no clinically significant effects on carbohydrate or lipid metabolism in man.

### 5.2 Pharmacokinetic properties

Fluconazole is a polar *bis*-triazole antifungal drug. Studies have shown that fluconazole exhibits specificity as an inhibitor of the fungal as opposed to mammalian cytochrome P-450 mediated reactions, including those involved in steroid biosynthesis and drug metabolism. Many of the clinical advantages of fluconazole are a result of its unique pharmacokinetic properties.

**Absorption:** The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes and do not appear to be affected by gastric pH. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration.

Essentially the entire administered drug reaches systemic circulation; thus, there is no evidence of first-pass metabolism of the drug. In addition, no adjustment in dosage is necessary when changing from p.o. to i.v. or *vice versa*.

Peak plasma concentrations (Cmax) in fasted normal volunteers occur rapidly following oral administration, usually between 1 and 2 hours of dosing with a terminal plasma elimination half-life of approximately 30 hours (range 20-50 hours) after oral administration. The long plasma elimination half-life provides the basis for once daily dosing with fluconazole in the treatment of fungal infections.

In fasted normal volunteers, administration of a single oral 150 mg dose of fluconazole

produced a mean Cmax of 2.70 μg/mL (range: 1.91 to 3.70 μg/mL).

In normal volunteers, oral bioavailability as measured by Cmax and AUC was not affected by food when fluconazole was administered as a single 50 mg capsule; however, Tmax was doubled.

**Distribution:** The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11%-12%) and is constant over the concentration range tested (0.1 mg/L to 10 mg/L). This degree of protein binding is not clinically meaningful.

A single oral 150 mg dose of fluconazole administered to 27 patients penetrated into vaginal tissue, resulting in tissue: plasma ratios ranging from 0.94 to 1.14 over the first 48 hours following dosing.

A single oral 150 mg dose of fluconazole administered to 14 patients penetrated into vaginal fluid, resulting in fluid: plasma ratios ranging from 0.36 to 0.71 over the first 72 hours following dosing.

**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 isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

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

**Metabolism and Excretion:** Fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Following administration of radiolabelled fluconazole, greater than 90% of the radioactivity is excreted in the urine. Approximately 11% of the radioactivity in urine is due to metabolites. An additional 2% of the total radioactivity is excreted in feces.

The pharmacokinetics of fluconazole does not appear to be affected by age alone but are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. There is no need to adjust single dose therapy for vaginal candidiasis because of impaired renal function.

**5.3Preclinical 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 10mg/kg/day. Male rats treated with 5 and 10mg/ kg/day had an increased incidence of hepatocellular adenomas approximately 2-7 times the recommended human dose.

**Mutagenesis:**

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of S.typhimurium and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in 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 fluconazole at 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 20mg/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. The effects on parturition in rats are consistent with the species specific estrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

Microcrystalline Cellulose BP

Calcium Hydrogen Phosphate BP

PVP K-30 USP

Colour Ponceau 4R IHS

Isopropyl Alcohol BP

Purified Water BP

Magnesium Stearate BP

Crospovidone BP

Croscarmellose Sodium BP

Purified Talc BP

**6.2 Incompatibilities**

None known

**6.3 Shelf life**

36 months from the date of manufacture

**6.4 Special precautions for storage**

Store below 30 °C in a dry place

Keep out of the reach of children.

Storage in the original package to protect from light and moisture.

Store the blister in the outer carton unit required for use.

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**6.5 Nature and contents of container**

1 x 1 Tablet in ALU-PVC Blister Pack

**6.6 Instructions for use and handling**

Keep out of the reach of children.

**7. MARKETING AUTHORISATION HOLDER**

**BDA HEALTHCARE PVT. LTD.,**

Plot No.: B-1, B-2, B-3, Near Gov. ITI MIDC, Parseoni – 441105,

Taluka: Parseoni, District: Nagpur, M.S., India.

**8. MARKETING AUTHORISATION NUMBER(S)**

06645/08300/NMR/2020

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

19.10.2021

**10. DATE OF REVISION OF THE TEXT**

02 July 2023