Approved Professional Information for Medicines for Human Use:

FLUCONAZOLE 50/150/200 mg AUSTELL CAPSULES

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

FLUCONAZOLE 50 mg AUSTELL CAPSULES

FLUCONAZOLE 150 mg AUSTELL CAPSULES

FLUCONAZOLE 200 mg AUSTELL CAPSULES

COMPOSITION

FLUCONAZOLE 50 mg AUSTELL:

Each capsule contains fluconazole 50 mg.

FLUCONAZOLE 150 mg AUSTELL:

Each capsule contains fluconazole 150 mg.

FLUCONAZOLE 200 mg AUSTELL:

Each capsule contains fluconazole 200 mg

PHARMACOLOGICAL CLASSIFICATION

A. 20.2.2 Antimicrobial (chemotherapeutic) agents. Fungicides.

PHARMACOLOGICAL ACTION

Fluconazole is a triazole antifungal agent. Fluconazole exerts its antifungal effect by inhibition of sterol 14-alpha-demethylase impairing the biosynthesis of ergosterol, the principal sterol in the fungal cell membrane. This damages the cell membrane, producing alterations in membrane function and permeability.

Pharmacokinetics:

Fluconazole is well absorbed after oral administration. Oral bioavailability is more than 90%. Oral bioavailability is not altered by foods or gastric acidity. The time to peak

plasma concentrations is 1 to 2 hours. Protein binding is low (12%). The elimination half-life in adults is approximately 30 hours and is increased in patients with impaired renal function. Fluconazole is primarily excreted by the kidneys. Approximately 80% of the dose is excreted unchanged in the urine. Fluconazole clearance is proportional to creatinine clearance. However, accumulation is significant over 15 days and concentrations may rise 2 to 3 fold. A small amount of fluconazole undergoes hepatic metabolism. Fluconazole is cleared from the body faster in children than in adults. The half-life in children is 23 hours. During the first 2 weeks of life the half-life is approximately 72 hours on day one and 47 hours on day 13.

INDICATIONS

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

- Systematic candidiasis.
- Oropharyngeal and oesophageal candidiasis.
- Prophylaxis of candidiasis in patients receiving cytotoxic chemotherapy and/or radiation therapy.

CONTRA-INDICATIONS

- Hypersensitivity to **FLUCONAZOLE AUSTELL**, other azole antifungal agents or to any of the excipients.
- Co-administration of terfenadine in patients receiving multiple doses of **FLUCONAZOLE AUSTELL** in doses of 400mg per day or greater. (See INTERACTIONS)
- Co-administration of cisapride. (See INTERACTIONS)
- Pregnancy and lactation. (See PREGNANCY AND LACTATION)
- Multiple dose therapy in contra-indicated in patients with renal impairment.
- Concurrent use with astemizole should be avoided.

WARNINGS

FLUCONAZOLE AUSTELL has been associated with cases of serious hepatotoxicity, including fatalities related to dose and duration of use, primarily in patients with serious underlying medical conditions. Hepatotoxicity may be reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during **FLUCONAZOLE AUSTELL** therapy should be monitored for the development of more serious hepatic injury. **FLUCONAZOLE AUSTELL** should be discontinued if clinical signs or symptoms consistent with the liver disease develop that may be attributed to **FLUCONAZOLE AUSTELL.** Patients have less frequently developed pruritus, rashes, urticaria, angioedema, dry skin, abnormal odour, exfoliative cutaneous reactions such as Steven-Johnson Syndrome and toxic epidermal necrolysis during treatment with **FLUCONAZOLE AUSTELL**. AIDS patients are more prone to the development of severe cutaneous reaction to many medicines. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and **FLUCONAZOLE AUSTELL** discontinued if bullous lesions or erythema multiforme develop.

INTERACTIONS

FLUCONAZOLE AUSTELL may interfere with the metabolism of some medicines if given concomitantly, mainly through inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. Coadministration of **FLUCONAZOLE AUSTELL** and medicines metabolized by cytochrome P450 can result in increased serum concentrations of the medicines metabolized by the same enzyme system.

FLUCONAZOLE AUSTELL increases plasma concentrations of the following medicines when given concomitantly:

- Warfarin - Anticoagulant effects are increased; resulting in an increase in prothrombin time/INR ratio. Monitoring of the prothrombin time is required and adjustment of the warfarin dose may be necessary.
- Sulfonylurea hypoglycaemics - The plasma concentration of these agents may be increased and hypoglycaemia can result. Blood glucose concentrations should be monitored and the dose of the sulfonylurea may need to be reduced.
- Phenytoin – Decreased metabolism of phenytoin, resulting in increased plasma concentrations and possible phenytoin toxicity.
- Theophylline – Decreased clearance of theophylline which leads to increased theophylline plasma concentrations and possible toxicity. Theophylline concentrations should be monitored.
- Zidovudine – Increased plasma concentrations of zidovudine. Patients should be monitored for zidovudine related adverse effects.
- Terfenadine – The concurrent use of terfenadine and doses of 400mg or more of **FLUCONAZOLE AUSTELL** is contra-indicated. If co-administration of terfenadine and **FLUCONAZOLE AUSTELL** at doses less than 400mg is considered essential terfenadine concentrations should be closely monitored. (See CONTRA-INDICATIONS) Astemizole has also been reported to interact with **FLUCONAZOLE AUSTELL** and concurrent use should be avoided. (See CONTRA-INDICATIONS)
- Cisapride – The concomitant administration of **FLUCONAZOLE AUSTELL** with cisapride is contra-indicated because of the possible increase in serum cisapride. Concentrations which can increase the risk of serious and life-threatening cardiac arrhythmias including torsade de pointes. (See CONTRA-INDICATIONS)
- Ciclosporin – Clinically significant rises in ciclosporin serum concentrations of two to threefold has been

observed in some patients when given fluconazole. Therefore ciclosporin plasma concentrations should be monitored in all patients receiving **FLUCONAZOLE AUSTELL.**

- Midazolam and triazolam - **FLUCONAZOLE AUSTELL** increases the serum concentrations of midazolam and triazolam and their psychomotor effects. This effect appears to be more pronounced following oral administration of **FLUCONAZOLE AUSTELL** than with **FLUCONAZOLE AUSTELL** administered intravenously. If these medicines are to be used concurrently a reduced dose of the benzodiazepine may be necessary and the patients should be monitored.
- Rifabutin – Increase in serum concentration of rifabutin which carries and increased risk of uveitis. Patients on this combination need to be carefully monitored.
- Tacrolimus – Tacrolimus concentrations are considerably increased by

FLUCONAZOLE AUSTELL. Patients on this combination need to have serum concentrations of tacrolimus be monitored and dose reduction is necessary.

The following medicine increases plasma concentrations of **FLUCONAZOLE AUSTELL** when given concomitantly:

- Hydrochlorothiazide

The following medicine decreases plasma concentrations of **FLUCONAZOLE AUSTELL** when given concomitantly:

- Rifampicin – Increased metabolism of **FLUCONAZOLE AUSTELL,** resulting in lower plasma concentrations of **FLUCONAZOLE AUSTELL.**

Other information on interactions:

Co-administration of fluconazole and nevirapine resulted in approximately 100% increase in nevirapine exposure as compared with historical data where nevirapine was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if nevirapine and **FLUCONAZOLE AUSTELL** are given concomitantly and patients should be monitored closely.

PREGNANCY AND LACTATION

The use of **FLUCONAZOLE AUSTELL** during pregnancy has resulted in congenital malformations and should be avoided. (See CONTRA-INDICATIONS)

FLUCONAZOLE AUSTELL should not be given to breast-feeding women. (See CONTRA-INDICATIONS)

FLUCONAZOLE AUSTELL is distributed into the breast milk at concentrations similar to those in plasma.

DOSAGE AND DIRECTIONS FOR USE

Cryptococcal Meningitis:

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

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

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 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 **FLUCONAZOLE AUSTELL** 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 the 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. Doses 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.

Recurring vaginal candidiasis:

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

Candida balanitis:

Adults: 150 mg administered as a single dose.

Dermal infection 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 be continued 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 **FLUCONAZOLE AUSTELL** 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

FLUCONAZOLE AUSTELL should be used with caution in patients with renal function impairment.

FLUCONAZOLE AUSTELL 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 **FLUCONAZOLE AUSTELL** after each dialysis session.

The patient's creatinine clearance (Ccr) can be estimated by using the following:

$$\text{Ccr male} = \frac{\text{Weight (kg)} \times (140-\text{age})}{72 \times \frac{\text{plasma creatinine (micromol/litre)}}{88}}$$

$$\text{Ccr female} = 0{,}85 \times \frac{\text{Weight (kg)} \times (140-\text{age})}{72 \times \text{plasma creatinine (micromol/litre)}}$$

The pharmacokinetics of **FLUCONAZOLE AUSTELL** have 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 **FLUCONAZOLE AUSTELL** 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 adjustment in dosage or dosing interval is required.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Haematological

Less frequent: Leucopenia, neutropenia, agranulocytosis and thrombocytopenia.

Central nervous system

- *More frequent:* Headache.
- *Less frequent*: Dizziness, vertigo, seizures, insomnia, nervousness, fatigue, rigors, malaise, hyperkinesias.

Endocrine /Metabolic

Less frequent: Hypokalaemia, hypercholesterolaemia, hypertriglyceridaemia.

Gastro-intestinal

- *More frequent:* Nausea, vomiting, abdominal pain, diarrhoea, flatulence.

- *Less frequent:* Taste perversion, dyspepsia, thirst.

Kidney/ Genito-urinary

Less frequent: Female sexual dysfunction, intermenstrual bleeding, menorrhagia, leukorrhea, polyuria.

Liver

- *More frequent:* Hepatotoxicity (including elevated serum concentrations of alkaline phosphatase, bilirubin, ALT and AST).
- *Less frequent:* Hepatic failure, hepatitis, hepatocellular nercosis, jaundice.

Musculoskeletal

Less frequent: hypertonia.

Ocular

Less frequent: Abnormal vision.

Skin

- *More frequent:* Rash.
- *Less frequent:* Alopecia, urticaria, dry skin, abnormal odour, exfoliative cutaneous reactions such as Steven-Johnson Syndrome and toxic epidermal necrolysis.

Other

Less frequent: Anaphylaxis, (including angio-oederma, facial oedema, pruritus) flushing.

Special precautions:

Liver function should be monitored periodically in all patients receiving continuous treatment with **FLUCONAZOLE AUSTELL** for more than one month or when a patient develops signs or symptoms suggestive of liver dysfunction. **FLUCONAZOLE AUSTELL** should be discontinued if abnormalities in enzyme value persist, worsen or if they are accompanied by symptoms of hepatotoxicity.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(see SIDE EFFECTS AND SPECIAL PRECAUTIONS)

Symptoms of overdose: The following have been reported with an overdose of **FLUCONAZOLE AUSTELL**: Insomnia, irritability, vomiting, diarrhoea, abdominal pains/ cramps, anorexia, bulging fontaneal, elevation of alkaline phosphates and gamma glutamyl transpetidases, increase in serum calcium, renal failure, fatigue, facial rash, skin erythema, generalized urticaria, arthralgia, itching, numbness of the tongue and depressed mood.

Treatment of overdose:

Treatment is symptomatic and supportive. There is no specific antidote.

FLUCONAZOLE AUSTELL is largely excreted in the urine. Forced diuresis may increase the elimination rate.

Elimination of **FLUCONAZOLE AUSTELL** can be facilitated by haemodialysis.

The concentration of **FLUCONAZOLE AUSTELL** can be decreased by about 50% by a three hour haemodialysis session.

IDENTIFICATION

FLUCONAZOLE 50 mg AUSTELL CAPSULES:

White to off white powder filled in Blue / White coloured hard gelatin capsules of size'4'.

FLUCONAZOLE 150 mg AUSTELL CAPSULES:

White to off white powder filled in Blue/ Blue coloured hard gelatin capsules of size'1'.

FLUCONAZOLE 200 mg AUSTELL CAPSULES:

White to off white powder filled in Purple / White coloured hard gelatin capsules of size '0'.

PRESENTATION

FLUCONAZOLE 50 mg AUSTELL CAPSULES:

Blister pack (Opaque PVDC coated PVC film & Aluminium foil) of 1 x 7 and 2 x 7 capsules.

Bulk pack (White HDPE Jars) of 100 capsules.

FLUCONAZOLE 150 mg AUSTELL CAPSULES:

Blister pack (Opaque PVDC coated PVC film & Aluminium foil) of 1 x 1 and 1 x 4 and 4 x 1 capsules.

Bulk pack (White HDPE Jars) of 100 capsules.

FLUCONAZOLE 200 mg AUSTELL CAPSULES:

Blister pack (Opaque PVDC coated PVC film & Aluminium foil) of 1 x 7, 2 x 7 and 4 x 7 capsules.

Bulk pack (White HDPE Jars) of 100 capsules.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light and moisture.

Keep blister packs in carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

FLUCONAZOLE 50 mg AUSTELL: 38/20.2.2/0013

FLUCONAZOLE 150 mg AUSTELL: 38/20.2.2/0058

FLUCONAZOLE 200 mg AUSTELL: 38/20.2.2/0014

NAME AND BUSINESS ADDRESS OF HOLDER OF THE CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG, 2193

DATE OF PUBLICATION OF PACKAGE THE INSERT

2 July 2004