SOUH AFRICAN PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ASPEN FLUCONAZOLE IV (infusion)

COMPOSITION

Each 1 ml infusion of ASPEN FLUCONAZOLE IV contains 2 mg of fluconazole.

Excipients:

Sodium chloride, water for injection

Sugar free

CATEGORY AND CLASS

A 20.2.2 Antimicrobial (chemotherapeutic) agents. Fungicides

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

Pharmacokinetic properties

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 74 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. ASPEN FLUCONAZOLE IV is indicated for the treatment of the following conditions in adults:

- Cryptococcal meningitis in mentally alert patients without localising neurological signs and as a follow-up therapy after Amphotericin B therapy.
- Maintenance therapy to prevent relapse of cryptococcal disease in patients with acquired immunodeficiency syndrome (AIDS).
- Systemic candidiasis.
- Oropharyngeal and oesophageal candidiasis.
- Prophylaxis of fungal infections in patients receiving cytotoxic chemotherapy and/or radiation therapy.
- Vaginal candidiasis - acute or recurrent infections and as prophylaxis to reduce the incidence of recurrent infections.
- Candidal balanitis.

- Dermatomycosis, including tinea pedis, tinea corporis, tinea cruris, tinea unguium (onychomycosis) and dermal *Candida* infections.

ASPEN FLUCONAZOLE IV is indicated for the treatment of the following conditions in children:

- Cryptococcal meningitis in mentally alert patients without localising neurological signs and as a follow up therapy after Amphotericin B therapy.
- Maintenance therapy to prevent relapse of cryptococcal disease in patients with acquired immunodeficiency syndrome (AIDS).
- Systemic candidiasis.
- Oropharyngeal and oesophageal candidiasis.
- Prophylaxis of candidiasis in patients receiving cytotoxic chemotherapy and/or radiation therapy.

CONTRAINDICATIONS

- Hypersensitivity to ASPEN FLUCONAZOLE IV, other azole antifungal agents or to any of the excipients.
- Co-administration of terfenadine in patients receiving multiple doses of ASPEN FLUCONAZOLE IV in doses of 400 mg per day or greater (see INTERACTIONS).
- Co-administration of cisapride (see INTERACTIONS).
- Pregnancy and lactation (see HUMAN REPRODUCTION).
- Multiple dose therapy is contraindicated in patients with renal impairment.
- Concurrent use with astemizole should be avoided.

WARNINGS AND SPECIAL PRECAUTIONS

ASPEN FLUCONAZOLE IV has been associated with cases of serious hepatotoxicity, including fatalities related to dose and duration of use, primarily in patients with serious

underlying medical conditions. Hepatotoxicity may be reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during ASPEN FLUCONAZOLE IV therapy should be monitored for the development of more serious hepatic injury. ASPEN FLUCONAZOLE IV should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to ASPEN FLUCONAZOLE IV.

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 ASPEN FLUCONAZOLE IV. 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 ASPEN FLUCONAZOLE IV discontinued if bullous lesions or erythema multiforme develop.

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

ASPEN FLUCONAZOLE IV 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.

INTERACTIONS

ASPEN FLUCONAZOLE IV may interfere with the metabolism of some medicines if given

concomitantly, mainly through inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9.

Co-administration of ASPEN FLUCONAZOLE IV and medicines metabolised by cytochrome P450 can result in increased serum concentrations of the medicines metabolised by the same enzyme system.

ASPEN FLUCONAZOLE IV 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 possibly 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 400 mg or more of ASPEN FLUCONAZOLE IV is contraindicated. If co-administration of terfenadine and ASPEN FLUCONAZOLE IV at doses less than 400 mg is considered essential, terfenadine concentrations should be closely monitored (see CONTRAINDICATIONS). Astemizole has also been reported to interact with ASPEN FLUCONAZOLE IV and

concurrent use should be avoided (see CONTRAINDICATIONS).

- Cisapride - The concomitant administration of ASPEN FLUCONAZOLE IV with cisapride is contraindicated 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 CONTRAINDICATIONS).
- 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 ASPEN FLUCONAZOLE IV.
- Midazolam and triazolam - ASPEN FLUCONAZOLE IV increases the serum concentrations of midazolam and triazolam and their psychomotor effects. This effect appears to be more pronounced following oral administration of ASPEN FLUCONAZOLE than with ASPEN FLUCONAZOLE IV administered intravenously. If these medicines are to be used concurrently a reduced dose of the benzodiazepine may be necessary and the patient should be monitored.
- Rifabutin - Increase in serum concentration of rifabutin which carries an increased risk of uveitis. Patients on this combination need to be carefully monitored.
- Tacrolimus - Tacrolimus concentrations are considerably increased by ASPEN FLUCONAZOLE IV. Patients on this combination need to have serum concentrations of tacrolimus monitored and dose reduction is necessary.

The following medicine increases plasma concentrations of ASPEN FLUCONAZOLE IV when given concomitantly:

- Hydrochlorothiazide

The following medicine decreases plasma concentrations of ASPEN FLUCONAZOLE IV when given concomitantly:

- Rifampicin - Increased metabolism of ASPEN FLUCONAZOLE IV, resulting in lower plasma concentrations of ASPEN FLUCONAZOLE IV.

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 ASPEN FLUCONAZOLE IV are given concomitantly and patients should be monitored closely.

HUMAN REPRODUCTION

The use of ASPEN FLUCONAZOLE IV during pregnancy has resulted in congenital malformations and should be avoided (see CONTRAINDICATIONS).

ASPEN FLUCONAZOLE IV should not be given to breastfeeding women (see CONTRAINDICATIONS).

ASPEN FLUCONAZOLE IV 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 clinical response. Duration of therapy is based on clinical and mycological response, but is usually 8 weeks, following Amphotericin B therapy and 10 weeks with ASPEN FLUCONAZOLE IV 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 ASPEN FLUCONAZOLE IV 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. 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 patient's 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 1 000 cells per mm^3.

Children over 4 weeks of age: 3 mg/kg/day 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 months to 12 months.

Candidal 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 ASPEN FLUCONAZOLE IV in children have not been established for the following indications: Recurrent vaginal candidiasis, candidal 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:

ASPEN FLUCONAZOLE IV should be used with caution in patients with renal function impairment. ASPEN FLUCONAZOLE IV 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 ASPEN FLUCONAZOLE IV after each dialysis session.

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

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

$$\text{Ccr (female)} = (0{,}85) \times \left[\frac{\text{Weight (kg) x (140 - age)}}{72 \times \frac{\text{(plasma creatinine (micromol/litre)}}{88} } \right]$$

The pharmacokinetics of ASPEN FLUCONAZOLE IV 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 ASPEN FLUCONAZOLE IV 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.

INTRAVENOUS INFUSION:

ASPEN FLUCONAZOLE IV is formulated in 0,9 % sodium chloride solution, each 200 mg (100 ml bottle) containing 15 mmol each of sodium and chloride ions.

Because ASPEN FLUCONAZOLE IV is available as a dilute saline solution, consideration should be given to the rate of fluid administration in patients requiring sodium or fluid restriction.

ASPEN FLUCONAZOLE IV infusion is compatible with the following administration fluids:

- Dextrose 5 % in water
- Ringer's lactate

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

ASPEN FLUCONAZOLE IV is for single use only. Discard any unused portion. The diluted solution is stable for 24 hours and should be stored between 18 °C and 24 °C.

SIDE EFFECTS

Frequently-occurring:

Blood and lymphatic system disorders:

- Leucopenia
- Neutropenia
- Agranulocytosis
- Thrombocytopenia

Central nervous system disorders:

- Headache

Gastrointestinal disorders:

- Nausea
- Vomiting
- Abdominal pain
- Diarrhoea
- Flatulence

Hepato-biliary disorders:

- Hepatotoxicity (including elevated serum concentrations of alkaline phosphatase, bilirubin, ALT and AST)

Skin and subcutaneous tissue disorders:

- Rash

Less frequently occurring:

Central nervous system disorders:

- Dizziness
- Vertigo
- Seizures
- Insomnia
- Nervousness
- Fatigue
- Rigors
- Malaise
- Hyperkinesia

Endocrine/Metabolism and nutrition disorders:

- Hypokalaemia
- Hypercholesterolaemia
- Hypertriglyceridaemia

Gastrointestinal disorders:

- Taste perversion
- Dyspepsia
- Thirst

Genito-urinary disorders:

- Female sexual dysfunction
- Intermenstrual bleeding
- Menorrhagia
- Leucorrhoea
- Polyuria

Hepato-biliary disorders:

- Hepatic failure
- Hepatitis
- Hepatocellular necrosis
- Jaundice

Musculo-skeletal and connective tissue disorders:

- Hypertonia

Eye disorders:

- Abnormal vision

Skin and subcutaneous tissue disorders:

- Alopecia
- Urticaria
- Dry skin
- Abnormal odour
- Exfoliative cutaneous reactions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis

Body as a whole:

- Anaphylaxis, (including angio-oedema, facial oedema, pruritus), flushing

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

(See WARNINGS AND SPECIAL PRECAUTIONS.)

Symptoms

The following have been reported with an overdose of ASPEN FLUCONAZOLE IV: Insomnia, irritability, vomiting, diarrhoea, abdominal pains/cramps, anorexia, bulging fontanel, elevation of alkaline phosphatase 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.

Treatment

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

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

Elimination of ASPEN FLUCONAZOLE IV can be facilitated by haemodialysis.

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

IDENTIFICATION

Transparent, colourless solution free from visible particles.

PRESENTATION

50 ml, 100 ml or 200 ml are packed in a transparent, colourless type I glass vial sealed with a grey, type I bromobutyl rubber stopper and a natural aluminium and polypropylene flip-off cap. The vial is labelled with a self-adhesive label and placed into a cardboard unit carton together with a leaflet.

200 ml are packed in a transparent polyvinyl chloride plastic bag with a connecting tube sealed with a bisfenol A polycarbonate plastic stopper and a twist-off closure. The bag is packed in an outer metallic overwrap.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Do not freeze.

Keep in original packaging until required for use.

Any unused portion of the solution must be discarded. The diluted solution is stable for 24 hours and should be stored between 18 °C and 24 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

A39/20.2.2/0572

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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