SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

MYCOREST 150 (capsules)

MYCOREST 200 (capsules)

COMPOSITION

Each **MYCOREST 150** capsule contains 150 mg fluconazole.

Each **MYCOREST 200** capsule contains 200 mg fluconazole.

Contains lactose monohydrate.

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 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.

MYCOREST 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.

CONTRAINDICATIONS

- Hypersensitivity to **MYCOREST**, other azole antifungal agents or to any of the excipients.
- **MYCOREST** should not be co-administered with medicines both known to prolong the QT interval and metabolised by CYP3A4, such as cisapride, astemizole, pimozide and quinidine.
- Co-administration of cisapride (see **INTERACTIONS**).
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Multiple dose therapy is contraindicated in patients with renal impairment.

- Concurrent use with astemizole should be avoided.

WARNINGS

MYCOREST 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 **MYCOREST** therapy should be monitored for the development of more serious hepatic injury. **MYCOREST** should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to **MYCOREST**.

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 **MYCOREST**. AIDS patients are more prone to the development of severe cutaneous reactions to many medicines. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and **MYCOREST** discontinued if bullous lesions or erythema multiforme develop.

INTERACTIONS

MYCOREST 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 **MYCOREST** and medicines metabolised by cytochrome P450 can result in increased serum concentrations of the medicines metabolised by the same enzyme system.

MYCOREST 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.
- *Sulphonylurea 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 sulphonylurea 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.
- *Astemizole* has also been reported to interact with **MYCOREST** and concurrent use should be avoided (see **CONTRAINDICATIONS**).
- *Cisapride* – The concomitant administration of **MYCOREST** 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 torsades de pointes (see **CONTRAINDICATIONS**).
- *Ciclosporin* – Clinically significant rises in ciclosporin serum concentrations of two to threefold have been observed in some patients when given fluconazole. Therefore, ciclosporin plasma concentrations should be monitored in all patients receiving **MYCOREST**.
- *Midazolam and triazolam* – **MYCOREST** increases the serum concentrations of midazolam and triazolam and their psychomotor effects. This effect appears to be pronounced following oral administration of **MYCOREST**. 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 **MYCOREST**. Patients on this combination need to have serum concentrations of tacrolimus monitored and dose reduction is necessary.

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

- *Hydrochlorothiazide*.

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

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

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 **MYCOREST** are given concomitantly and patients should be monitored closely.

PREGNANCY AND LACTATION

The use of **MYCOREST** during pregnancy has resulted in congenital malformations and should be avoided (see **CONTRAINDICATIONS**).

MYCOREST should not be given to breastfeeding women (see **CONTRAINDICATIONS**).

MYCOREST 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 mycological response, but is usually 8 weeks, following amphotericin B therapy and 10 weeks with **MYCOREST** monotherapy.

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

Adults: Up 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.

Duration of therapy is based on clinical and mycological response.

Oropharyngeal candidiasis:

To prevent relapse in AIDS patients: 150 mg of **MYCOREST** may be given once a week.

Oesophageal candidiasis:

Adults: Initial dose is 200 mg on the first day; followed by 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.

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

Adults: Up 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 1000 cells per mm^3.

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.

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 re-grow and toenails 6 to 12 months.

Children: Safety and efficacy of **MYCOREST** in children have 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: 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 (see **DOSAGE IN RENAL FAILURE**).

DOSAGE IN RENAL FAILURE

MYCOREST should be used with caution in patients with renal function impairment. **MYCOREST** 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 the patient is not receiving dialysis, this dosage form can not be given.

Patients on regular haemodialysis should receive a standard dose of **MYCOREST** after each dialysis session.

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

$$\text{Ccr male} = \frac{\text{mass (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/dl)}}$$

$$\text{Ccr female} = \frac{\text{0,85 x mass (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/dl)}}$$

The pharmacokinetics of **MYCOREST** 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 **MYCOREST** 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.
- 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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects:

Blood and the lymphatic system disorders:

Less frequent: Agranulocytosis and thrombocytopenia.

Frequency unknown: Leucopenia, neutropenia.

Immune system disorders:

Less frequent: Hypersensitivity.

Frequency unknown: Anaphylaxis (including angioedema, facial oedema, pruritus).

Metabolism and nutrition disorders:

Frequency unknown: Hypokalaemia, hypercholesterolaemia, hypertriglyceridaemia.

Nervous system disorders:

Frequency unknown: Headache, dizziness, vertigo, seizures, insomnia, nervousness, fatigue, rigors, malaise, hyperkinesia.

Eye disorders:

Less frequent: Photophobia.

Frequency unknown: Abnormal vision.

Cardiac disorders:

Frequency unknown: QT prolongation, torsades de pointes.

Gastrointestinal disorders:

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

Less frequent: Taste perversion, dyspepsia, thirst.

Hepato-biliary disorders:

Less frequent: Hepatotoxicity (including elevated serum concentrations of alkaline phosphatase, bilirubin, ALT and AST).

Frequency unknown: Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Skin and subcutaneous tissue disorders:

Less frequent: Exfoliative cutaneous reactions such as Stevens-Johnson syndrome and rash.

Frequency unknown: Alopecia, urticaria, dry skin, abnormal odour, toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Hypertonia.

Renal and urinary disorders:

Frequency unknown: Polyuria.

Reproductive system and breast disorders:

Frequency unknown: Female sexual dysfunction, intermenstrual bleeding, menorrhagia, leucorrhoea.

General disorders and administrative site conditions:

Frequency unknown: Flushing.

Special precautions:

Liver function should be monitored periodically in all patients receiving continuous treatment with **MYCOREST** for more than one month, or when a patient develops signs or symptoms suggestive of

liver dysfunction. **MYCOREST** should be discontinued if abnormalities in enzyme values persist, worsen or if they are accompanied by symptoms of hepatotoxicity.

MYCOREST 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.

MYCOREST contains lactose monohydrate and should not be given in patients with rare hereditary problems, or a history of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

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 **MYCOREST**: 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.

Treatment of overdose:

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

MYCOREST is largely excreted in the urine. Forced diuresis may increase the elimination rate. Elimination of **MYCOREST** can be facilitated by haemodialysis. The concentration of **MYCOREST** can be decreased by about 50 % by a three hour haemodialysis session.

IDENTIFICATION

MYCOREST 150: Size ‘1’ hard gelatine capsule with opaque powder blue coloured cap and opaque white body printed with ‘150 mg’ and ‘Z-09’ containing a white to off-white powder.

MYCOREST 200: Size ‘0’ hard gelatine capsule with purple coloured cap and powder blue coloured body printed with ‘200 mg’ and ‘Z-10’ containing a white to off-white powder.

PRESENTATION

MYCOREST 150 capsules are packed in aluminium, white opaque PVC/PVdC blister strips containing 10, 4 or 1 capsule per blister. The blister strips will be packed in an outer carton containing 5 x 10 blister strips (50 capsules), 1 x 4 blister strips (4 capsules) or 1 capsule.

MYCOREST 200 capsules are packed in aluminium, white opaque PVC/PVdC blister strips containing 10 or 7 capsules per blister. The blister strips will be packed in an outer carton containing 5 x 10 blister strips (50 capsules), 4 x 7 blister strips (28 capsules) or 3 x 10 capsules (30 capsules).

STORAGE INSTRUCTIONS

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

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS

MYCOREST 150: A39/20.2.2/0534

MYCOREST 200: A40/20.2.2/0438

NAME AND BUSINESS ADDRESS OF HOLDER OF THE REGISTRATION CERTIFICATE

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