SCHEDULING STATUS

S4

PROPRIETARY NAME [AND DOSAGE FORM]:
RALMIENT 50 mg (Capsules)
RALMIENT 100 mg (Capsules)
RALMIENT 150 mg (Capsules)
RALMIENT 200 mg (Capsules)

COMPOSITION:
RALMIENT 50 mg:
Each capsule contains 50 mg fluconazole.
Contains sugar: Lactose Monohydrate
RALMIENT 100 mg:
Each capsule contains 100 mg fluconazole.
Contains sugar: Lactose Monohydrate
RALMIENT 150 mg:
Each capsule contains 150 mg fluconazole.
Contains sugar: Lactose Monohydrate
RALMIENT 200 mg:
Each capsule contains 200 mg fluconazole.
Contains sugar: 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 food 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 unchanged 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.

RALMIENT 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

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

WARNINGS:
RALMIENT 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 **RALMIENT** therapy should be monitored for the development of more serious hepatic injury. **RALMIENT** should be discontinued if clinical signs or symptoms consistent with the liver disease develop that may be attributable to **RALMIENT**.
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 **RALMIENT**. 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 **RALMIENT** discontinued if bullous lesions or erythema multiforme develop.

INTERACTIONS:
RALMIENT 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 **RALMIENT** and medicines metabolised by cytochrome P450 can result in increased serum concentrations of the medicines metabolised by the same enzyme system.
RALMIENT 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 **RALMIENT** is contraindicated. If co•administration of terfenadine and **RALMIENT** 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 **RALMIENT** and concurrent use should be avoided. (see **CONTRAINDICATIONS**)
- Cisapride – The concomitant administration of **RALMIENT** 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 three•fold has been observed in some patients when given fluconazole. Therefore ciclosporin plasma concentrations should be monitored in all patients receiving **RALMIENT.**
- Midazolam and triazolam – **RALMIENT** increases the serum concentrations of midazolam and triazolam and their psychomotor effects. This effect appears to be more pronounced following oral administration of **RALMIENT** than with fluconazole 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 **RALMIENT.** 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 **RALMIENT** when given concomitantly:
- Hydrochlorothiazide

The following medicine decreases plasma concentrations of concentrations of **RALMIENT** when given concomitantly:
- Rifampicin – Increased metabolism of **RALMIENT**, resulting in lower plasma concentrations of **RALMIENT**.

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 excercised if nevirapine and **RALMIENT** are given concomitantly and patients should be monitored closely.

PREGNANCY AND LACTATION:
The use of **RALMIENT** during pregnancy has resulted in congenital malformations and should be avoided. (See **CONTRAINDICATIONS**)

RALMIENT should not be given to breast•feeding women. (See **CONTRAINDICATIONS**).
RALMIENT is distributed into the breast milk at concentrations similar to those in plasma.
DOSAGE AND DIRECTIONS FOR USE (FOR ALL FORMULATIONS):
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 **RALMIENT** 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 **RALMIENT** 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 continues for 7 days after the neutrophil count rises about 1 000 cells per mm^3.
Children over 4 weeks of age: 3 to 12 mg/kg/day depending on the extent and duration of the induced neutropenia.

Vaginal Candidiasis
Adults: 150 mg administered as a single dose.

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

Candida balanitis
Adults: 150 mg administered as a single dose.

Dermal infections including tinea pedis, tinea corporis, tinea cruris, tinea unguium (onychomycosis) and dermal candida infections
Adults: 150 mg administered as a single dose once a week.
Duration of treatment is usually 2 to 4 weeks but tinea pedis may require up to 6 weeks of treatment. For tinea unguium, treatment should continue until the infected nail grows out and is replaced with an uninfected nail. Fingernails generally require 3 to 6 months to regrow and toenails 6 to 12 months.

Safety and efficacy of **RALMIENT** 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 of dosing interval is required.

DOSAGE IN RENAL FAILURE
RALMIENT should be used with caution in patients with renal function impairment. **RALMIENT** 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 **RALMIENT** after each dialysis session.
When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance in adults:

$$\text{Ccr male} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 ml)}}$$

Ccr female = 0,85 x above value

Although the pharmacokinetics of fluconazole has not been studied in children with renal insufficiency, dosage reduction in children with renal insufficiency should parallel that recommended for adults.
The pharmacokinetics of **RALMIENT** 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 **RALMIENT** 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.

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, hyperkinesia

Endocrine/Metabolic:
- *Less frequent:* Hypokalaemia, hypercholesterolaemia, hypertriglyceridaemia

Gastrointestinal:
- *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, leukorrhoea, polyuria

Liver:
- *More frequent:* Hepatotoxicity (including elevated serum concentrations of alkaline phosphatase, bilirubin, ALT and AST)
- *Less frequent:* Hepatic failure, hepatitis, hepatocellular necrosis, 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•oedema, facial oedema, pruritus), flushing

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

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 **RALMIENT:** 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 a ntidote. **R ALMIENT** i s largely excreted in the urine. Forced diuresis may increase the elimination rate. Elimination of **RALMIENT** can be facilitated by haemodialysis. The concentration of **RALMIENT** can be decreased by about 50 % by a three hour haemodialysis session.

IDENTIFICATION:
RALMIENT 50 MG: Size 4 hard gelatin capsules with white body and a dark blue opaque cap.. The capsules contain a white to off-white powder.
RALMIENT 100 MG: Size 2 hard gelatin capsules with white opaque body and a blue opaque cap. The capsules contain a white to off-white powder.
RALMIENT 150 MG: Size 1 hard gelatin capsules with dark blue opaque body and a dark blue opaque cap. The capsules contain a white to off•white powder.
RALMIENT 200 MG: Size 0 hard gelatin capsules with white opaque body and a white opaque cap. The capsules contain a white to off-white powder.

PRESENTATION:
PVC/PVDC/Aluminium blisters containing 1, 4, 7 or 10 or 14 capsules.
1, 4, 7, 10, 14, 20, 28, 30, 50, 100 capsules are packed in a cardboard carton.

STORAGE INSTRUCTIONS:
Store at or below 25 ºC. Keep the blisters in the carton until required for use. **KEEP OUT OF REACH OF CHILDREN**.

REGISTRATION NUMBERS
RALMIENT 50 MG: A38/20.2.2/0556
RALMIENT 100 MG: A38/20.2.2/0557
RALMIENT 150 MG: A38/20.2.2/0558
RALMIENT 200 MG: A38/20.2.2/0559

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
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DATE OF PUBLICATION OF THE PACKAGE INSERT: 23 July 2004

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