APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

AURO FLUCONAZOLE 50 mg (Capsule)

AURO FLUCONAZOLE 100 mg (Capsule)

AURO FLUCONAZOLE 150 mg (Capsule)

AURO FLUCONAZOLE 200 mg (Capsule)

COMPOSITION:

AURO FLUCONAZOLE 50 mg

Each capsule contains 50 mg fluconazole

AURO FLUCONAZOLE 100 mg

Each capsule contains 100 mg fluconazole

AURO FLUCONAZOLE 150 mg

Each capsule contains 150 mg fluconazole

AURO FLUCONAZOLE 200 mg

Each capsule contains 200 mg fluconazole

The other ingredients of **AURO FLUCONAZOLE** are lactose monohydrate, maize starch, sodium lauryl sulphate, silica, colloidal anhydrous and magnesium stearate. The empty hard gelatin capsule shell consists of gelatin, sodium lauryl sulfate and titanium dioxide (C.I. No: 77891). The capsules are printed with edible ink, shellac and yellow iron oxide (C.I. No: 77492).

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.2 Fungicides

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Antifungal Activity:

Fluconazole is a fluorinated bistriazole, a member of the triazole antifungal agents, and inhibitor of fungal steroid activity.

Fluconazole has activity against *Candida albicans, Candida tropicalis, C. glabrata, C. neoformans, B. dermatitidis, H. capsulatum, C. immitis, Paracoccidioides brasiliensis,* and ringworm fungi (dermatophytes).

Pharmacokinetics:

Absorption, Distribution and Excretion:

Fluconazole is almost completely absorbed from the gastrointestinal tract. Concentrations in plasma are essentially the same whether fluconazole is given orally or intravenously, and bioavailability is not altered by food or gastric acidity. Peak plasma concentrations are 4 to 8 µg/ml after repetitive doses of 100 mg. Renal excretion accounts for over 90 % of elimination, and the elimination half-life is 25 to 30 hours. Fluconazole diffuses readily into body fluids, including sputum and saliva; concentrations in CSF are 50 % to 90 % of the simultaneous values in plasma. The dosage interval should be increased from 24 to 48 hours with a creatinine clearance of 1 to 40 ml/min and to 72 hours at 10 to 20 ml/min. A dose of 100 to 200 mg should be given after each haemodialysis. About 11 % to 12 % of plasma component is protein bound.

INDICATIONS:

AURO FLUCONAZOLE is indicated for the treatment of the following conditions in adults: Cryptococcal meningitis and maintenance therapy to prevent relapse of cryptococcal disease in patients with a

1. Systemic candidasis.
2. Oropharyngeal and oesophageal candidiasis.
3. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy and radiotherapy.

CONTRA-INDICATIONS:

- **AURO FLUCONAZOLE** should not be used in patients with known hypersensitivity to fluconazole or to any of the ingredients or to related azole compounds.
- Pregnancy and lactation (see **PREGNANCY AND LACTATION**).
- Multiple dose therapy is contraindicated in patients with renal impairment.
- Co-administration of **AURO FLUCONAZOLE** with medicines metabolised by CYP 3A4 and are known to prolong QT interval, such as cisapride, astemizole, pimozide and quinidine (see **INTERACTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS:

Warnings

Hepatic Function:

Fluconazole such as in **AURO FLUCONAZOLE** has been associated with 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. Hepatotoxicity may be reversible on discontinuation of **AURO FLUCONAZOLE** therapy. Patients who develop abnormal liver function tests during **AURO FLUCONAZOLE** therapy should be monitored for the development of more serious hepatic injury. **AURO FLUCONAZOLE** should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to fluconazole.

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 **AURO FLUCONAZOLE** discontinued if bullous lesions or erythema multiforme develop.

Special Precautions:

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

Effects on Ability to Drive and Use of Machinery:

AURO FLUCONAZOLE may cause abnormal vision which may affect ability to drive and use machinery.

INTERACTIONS:

Fluconazole has been shown to prolong prothrombin times/INR in subjects receiving warfarin. Bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melena) have been reported, in association with increases in prothrombin time/INR in patients receiving fluconazoles such as in **AURO FLUCONAZOLE** concurrently with warfarin. In concomitant treatment of **AURO FLUCONAZOLE** and warfarin the dose of anticoagulant should be carefully titrated and the prothrombin time/INR should be carefully monitored. Particular attention should be paid to such patients requiring minor oral surgery and dental procedures.

Benzodiazepines (Short Acting): Concurrent oral administration of midazolam and fluconazole resulted in substantial increases in midazolam concentrations and its psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy (e.g. midazolam, triazolam) is necessary in patients on treatment with **AURO-FLUCONAZOLE**, a reduction of the benzodiazepine dosage should be considered and patients should be appropriately monitored. Fluconazole such as in **AURO FLUCONAZOLE** has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas.

No clinically significant interactions have been seen with co-administration of oral contraceptives, or cimetidine. No adverse effect has been seen on endogenous steroid levels or on ACTH stimulated cortisol response.

A kinetic study in renal transplant patients found fluconazole 200 mg daily to slowly increase ciclosporin concentrations. However, in another multiple dose study with 100 mg daily, fluconazole did not affect ciclosporin levels in patients with bone marrow transplants. Ciclosporin plasma concentration monitoring in patients receiving **AURO FLUCONAZOLE** is recommended.

Co-administration of multiple doses of hydrochlorothiazide may increase the plasma concentrations of fluconazole such as in **AURO FLUCONAZOLE**.

Concomitant administration of **AURO FLUCONAZOLE** and phenytoin may increase the levels of phenytoin to a clinical significant degree.

Concomitant administration of **AURO FLUCONAZOLE** and theophylline may increase the risk of theophylline toxicity due to a fluconazole induced decrease in plasma theophylline clearance.

Concomitant administration of **AURO FLUCONAZOLE** and rifampicin may result in a 25 % decrease in the AUC and 20 % shorter half-life of fluconazole.

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, cross-over study examined zidovudine levels in HIV 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 **AURO FLUCONAZOLE** in combination with zidovudine should be monitored for the development of zidovudine-related adverse reactions.

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

Cisapride: There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were co-administered. Co-administration of cisapride is contraindicated in patients receiving **AURO-FLUCONAZOLE**.

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 co-administered. Patients receiving rifabutin and **AURO FLUCONAZOLE** concomitantly should be carefully monitored.

Tacrolimus: There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom **AURO FLUCONAZOLE** and tacrolimus were co-administered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored for changes in plasma concentrations of tacrolimus and/or nephro- and neurotoxicity.

The use of **AURO FLUCONAZOLE** in patients concurrently taking astemizole or other medicines metabolised by the cytochrome P-450 system may be associated with elevations in serum levels of these medicines. In the absence of definitive information, caution should be used when co-administering **AURO FLUCONAZOLE**. Patients should be carefully monitored (see **WARNINGS AND SPECIAL PRECAUTIONS**).

PREGNANCY AND LACTATION:

Use during pregnancy and lactation:

There are no adequate and well controlled studies which assessed the safety of fluconazole treatment in pregnant women. There have been reports of congenital abnormalities in infants whose mothers were treated with fluconazole. The relationship between fluconazole use and these events is unclear.

Lactation, as fluconazole is found in breast milk at concentrations similar to plasma.

DOSAGE AND DIRECTIONS FOR USE:

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.

Use in Adults:

1. For cryptococcal meningitis the usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response of the patient this dose may be increased to 400 mg daily. Usually, duration of treatment for cryptococcal meningitis is 6-8 weeks.

   For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient received a full course of primary therapy, **AURO FLUCONAZOLE** may be administered at a daily dose of 100 to 200 mg.
2. For systemic candidiasis the usual dose is 400 mg on the first day followed by 200 mg daily. Depending on the clinical response, the dose may be increased to 400 mg daily. Duration of treatment is based upon the clinical response.

3. For oropharyngeal candidiasis, the usual dose is 50 to 100 mg once daily for 7- 14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function.

   For the prevention of relapse of oropharyngeal candidiasis in patients with AIDS, after the patient receives a full course of primary therapy, **AURO FLUCONAZOLE** may be administered at a 150 mg once weekly dose.

   For oesophageal candidiasis, the recommended dose is 200 mg on the first day, followed by 100 mg to 200 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with oesophageal candidiasis should be treated for a minimum of three weeks and for at least two weeks following resolution of symptoms.
4. The recommended **AURO FLUCONAZOLE** dosage for the prevention of candidiasis is 50 mg to 400 mg once daily, based on the patient's risk for developing fungal infections. For patients at high risk of systemic infection e.g. patients who are anticipated to have profound or prolonged neutropenia, a dose of 400 mg once daily has been used. **AURO FLUCONAZOLE** administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells per mm^3.

Use in the Elderly:

Where there is no evidence of renal impairment, normal dosage recommendations should be adopted.

Use in Children:

This formulation is not suitable for dosages < 50 mg/kg.

Dosage in Patients with Impaired Renal Function:

Fluconazole is cleared primarily by renal excretion as unchanged compound. No adjustments in single dose therapy are necessary. Multiple-dose therapy should be carefully monitored in patients with renal impairment.

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

DOSAGE AND ADMINISTRATION:

AURO FLUCONAZOLE

Creatinine Clearance (ml/min)	Percent of Recommended Dose
>50	100 %
<50	50 %
Regular haemodialysis	100 % after each dialysis

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition. 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:

$$\text{eGFR}^* \text{ (ml/min)} = \frac{(140 - \text{age}) \times \text{Wt (kg)}}{S_{cr} \text{ (µmol/litre)}}$$

* For females multiply the GFR by 0,85.

SIDE EFFECTS:

Blood and the lymphatic system disorders:

Less frequent: Thrombocytopenia.

The following side effects have been reported but the frequencies are unknown: Neutropenia, leucopenia.

Immune system disorders:

The following side effects have been reported but the frequencies are unknown: Anaphylaxis, angioedema.

Metabolism and nutritional disorders:

The following side effects have been reported but the frequencies are unknown: Hypertriglyceridemia.

Nervous system disorders:

The following side effects have been reported but the frequencies are unknown:

Seizures.

Gastrointestinal disorders:

Less frequent: Abdominal pain, vomiting, nausea, diarrhoea and flatulence.

The following side effects have been reported but the frequencies are unknown:

Taste perversion, constipation, dyspepsia.

Hepato-biliary disorders:

The following side effects have been reported but the frequencies are unknown:

Hepatitis, liver failure.

Skin and subcutaneous tissue disorders:

Less frequent: Stevens-Johnson syndrome

The following side effects have been reported but the frequencies are unknown:

Alopecia, toxic epidermal necrolysis, pruritus, urticaria.

Reproductive system and breast disorders:

The following side effects have been reported but the frequencies are unknown:

Menstrual disorders.

Eye disorders:

The following side effects have been reported but the frequencies are unknown:

Abnormal vision.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The following events may occur with an overdosage of **AURO FLUCONAZOLE**: insomnia, irritability, vomiting, diarrhoea, abdominal pain/cramps, anorexia, bulging fontanel, elevation of alkaline phosphatase and gamma glutamyl transpeptidase, increase in serum calcium, renal failure, fatigue, facial rash, skin erythema, generalised urticaria, arthralgia, itching, numbness of the tongue and distressed mood.

In the advent of overdosage, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

Fluconazole is largely excreted in the urine; forced diuresis would probably increase the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50 %.

IDENTIFICATION:

AURO FLUCONAZOLE 50 mg:

White to off-white opaque/white to off-white opaque size ‘4’ hard gelatin capsule filled with white to off-white powder and imprinted with ‘E’ on white to off-white opaque cap and ‘95’ on white to off-white opaque body with yellow ink.

AURO FLUCONAZOLE 100 mg:

White to off-white opaque/white to off-white opaque size ‘2’ hard gelatin capsule filled with white to off-white powder and imprinted with ‘E’ on white to off-white opaque cap and ‘96’ on white to off-white opaque body with yellow ink.

AURO FLUCONAZOLE 150 mg:

White to off-white opaque/white to off-white opaque size ‘1’ hard gelatin capsule filled with white to off-white powder and imprinted with ‘E’ on white to off-white opaque cap and ‘97’ on white to off-white opaque body with yellow ink.

AURO FLUCONAZOLE 200 mg:

White to off-white opaque/white to off-white opaque size '0' hard gelatin capsule filled with white to off-white powder and imprinted with 'E' on white to off-white opaque cap and '98' on white to off-white opaque body with yellow ink.

PRESENTATION:

AURO FLUCONAZOLE 50 mg:

1. **Pack size: 14's Blister Pack**

   Capsules are packed in clear 250 micron PVC coated with 60 gsm PVdc and printed aluminium foil with 7 gsm heat seal lacquer.

   Each carton contains 1 blister of 14 capsules each.

2. **Pack size: 30's HDPE Container Pack**

   Capsules are packed in a 40 ml white opaque HDPE container with a white opaque polypropylene stock ribbed closure with induction seal wad.

   Each container contains 30 capsules.

AURO FLUCONAZOLE 100 mg:

1. **Pack size: 30's Blister Pack**

   Capsules are packed in clear 250 micron PVC coated with 60 gsm PVdc and printed aluminium foil with 7 gsm heat seal lacquer.

   Each carton contains 3 blisters of 10 capsules each.

2. **Pack size: 30's HDPE Container Pack**

   Capsules are packed in a 40 ml white opaque HDPE container with a white opaque polypropylene stock ribbed closure with induction seal wad.

   Each container contains 30 capsules.

AURO FLUCONAZOLE 150 mg:

1. **Pack size: 1's Blister Pack**

   Capsules are packed in clear 250 micron PVC coated with 60 gsm PVdc and printed aluminium foil with 7 gsm heat seal lacquer.

Each carton contains 1 blister of 1 capsule each.

2. **Pack size: 4's Blister Pack**

Capsules are packed in clear 250 micron PVC coated with 60 gsm PVdc and printed aluminium foil with 7 gsm heat seal lacquer.

Each carton contains 1 blister of 4 capsules each.

AURO FLUCONAZOLE 200 mg:

1. **Pack size: 30's Blister Pack**

Capsules are packed in clear 250 micron PVC coated with 60 gsm PVdc and printed aluminium foil with 7 gsm heat seal lacquer.

Each carton contains 3 blisters of 10 capsules each.

2. **Pack size: 30's HDPE Container Pack**

Capsules are packed in a 60 ml white opaque HDPE container with a white opaque polypropylene stock ribbed closure with induction seal wad.

Each container contains 30 capsules.

STORAGE INSTRUCTIONS:

1) **Blister:**

Store at or below 25 °C. Keep blisters in the original carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

2) **HDPE Container:**

Store at or below 25 °C. Keep well closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

AURO FLUCONAZOLE 50 mg: 43/20.2.2/0560

AURO FLUCONAZOLE 100 mg: 43/20.2.2/0561

AURO FLUCONAZOLE 150 mg: 43/20.2.2/0562

AURO FLUCONAZOLE 200 mg: 43/20.2.2/0563

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

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