PACKAGE INSERT FOR CIPLA-FLUCONAZOLE 50, CIPLA-FLUCONAZOLE 150, CIPLA-FLUCONAZOLE 200 CAPSULES

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-FLUCONAZOLE 50 (Capsule)

CIPLA-FLUCONAZOLE 150 (Capsule)

CIPLA-FLUCONAZOLE 200 (Capsule)

COMPOSITION:

The chemical name of **CIPLA-FLUCONAZOLE** (fluconazole), a bis-triazole, is 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol. Fluconazole has a molecular weight of 306.3. It is a white to off-white crystalline powder which is sparingly soluble in water and saline.

CIPLA-FLUCONAZOLE 50: Each capsule contains 50 mg **fluconazole.**

CIPLA-FLUCONAZOLE 150: Each capsule contains 150 mg **fluconazole.**

CIPLA-FLUCONAZOLE 200: Each capsule contains 200 mg **fluconazole.**

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:

Anti-infective therapy should be adjusted once the results of the cultures and other laboratory studies become available.

CIPLA-FLUCONAZOLE 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).
- Oropharyngeal and oesophageal candidiasis.
- Systemic 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 corporis, tinea cruris, tinea pedis, tinea unguium (onychomycosis) and dermal candida infections.

CIPLA-FLUCONAZOLE 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).
- Oropharyngeal and oesophageal candidiasis.
- Systemic candidiasis.

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

CONTRA-INDICATIONS:

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

WARNINGS:

CIPLA-FLUCONAZOLE 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. This hepatotoxicity may be reversible when therapy is discontinued. Any patients who develop abnormal liver function tests, while taking **CIPLA-FLUCONAZOLE**, should be carefully monitored for the development of more serious hepatic injury. Should signs and symptoms consistent with liver disease develop, that may

be attributable to **CIPLA-FLUCONAZOLE, CIPLA-FLUCONAZOLE** should be discontinued.

Less frequently, patients have developed rashes, urticaria, pruritus, dry skin, abnormal odour, angioedema and exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with **CIPLA-FLUCONAZOLE**. Patients with AIDS are more prone to the development of severe cutaneous reactions to numerous medicines. Should patients with systemic/invasive fungal infections develop rashes, they should be monitored closely, and if bullous lesions or erythema multiforme develop, **CIPLA-FLUCONAZOLE** must be discontinued.

INTERACTIONS:

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

CIPLA-FLUCONAZOLE 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 **CIPLA-FLUCONAZOLE** is contra-indicated. If co-administration of terfenadine and **CIPLA-FLUCONAZOLE** at doses less than 400 mg is considered, essential terfenadine concentrations should be closely monitored (see **CONTRA-INDICATIONS**). Astemizole has also been reported to interact with **CIPLA-FLUCONAZOLE** and concurrent use should be avoided (see **CONTRA-INDICATIONS**).
- Cisapride - The concomitant administration of **CIPLA-FLUCONAZOLE** 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 **CIPLA-FLUCONAZOLE**.

- Midazolam and triazolam - **CIPLA-FLUCONAZOLE** increases the serum concentrations of midazolam and triazolam and their psychomotor effects. This effect appears to be more pronounced following oral administration of **CIPLA-FLUCONAZOLE** 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 **CIPLA-FLUCONAZOLE**. Patients on this combination need to have serum concentrations of tacrolimus monitored and dose reduction is necessary.

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

- Hydrochlorothiazide

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

- Rifampicin - Increased metabolism of **CIPLA-FLUCONAZOLE E**, resulting in lower plasma concentrations of **CIPLA-FLUCONAZOLE**.

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 **CIPLA-FLUCONAZOLE** are given concomitantly and patients should be monitored closely.

PREGNANCY AND LACTATION:

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

CIPLA-FLUCONAZOLE should not be given to breast-feeding women (see **CONTRA-INDICATIONS**).

CIPLA-FLUCONAZOLE 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 **CIPLA-FLUCONAZOLE** 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 daily.

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 **CIPLA-FLUCONAZOLE** 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 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.

Recurrent 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 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 **CIPLA-FLUCONAZOLE** 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:

CIPLA-FLUCONAZOLE should be used with caution in patients with renal function impairment. **CIPLA-FLUCONAZOLE** 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 < 50ml/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 **CIPLA-FLUCONAZOLE** after each dialysis session.

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

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

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

The pharmacokinetics of **CIPLA-FLUCONAZOLE** 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 **CIPLA-FLUCONAZOLE** 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 he 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:

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

Endocrine/Metabolic:

- *Less frequent*: Hypokalaemia, hypercholesterolaemia, hypertriglyceridaemia.

Gastrointestinal:

- *Frequent*: Nausea, vomiting, abdominal pain, diarrhoea, flatulence.
- *Less frequent*: Taste perversion, dyspepsia, thirst.

Kidney/Genitourinary:

- *Less frequent*: Female sexual dysfunction, intermenstrual bleeding, menorrhagia, leukorrhoea, polyuria.

Liver:

- *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:

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

Other:

- *Less frequent*: Anaphylaxis (including angioedema, facial oedema, pruritus), flushing.

Special precautions:

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

CIPLA-FLUCONAZOLE 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 **CIPLA-FLUCONAZOLE:** Irritability, insomnia, depressed mood, numbness of the tongue, bulging fontanel, anorexia, vomiting, abdominal pains/cramps, diarrhoea, fatigue, itching, facial rash, generalised urticaria, skin erythema, arthralgia, renal failure, elevation of alkaline phosphatase and gamma-glutamyl transpeptidases and increase in serum calcium.

Treatment of overdose:

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

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

Elimination of **CIPLA-FLUCONAZOLE** can be facilitated by haemodialysis.

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

IDENTIFICATION:

CIPLA-FLUCONAZOLE 50 Capsules:	White powder filled in hard gelatin capsule of size ‘4’ with white opaque body and sky blue opaque cap having ‘FCZ 50’ printed on body and cap in black linear pattern.

CIPLA-FLUCONAZOLE 150 Capsules:	White powder filled in hard gelatin capsule of size ‘1’ with sky blue opaque body and sky blue opaque cap having ‘FCZ 150’ printed on body and cap in black linear pattern.
CIPLA-FLUCONAZOLE 200 Capsules:	White powder filled in hard gelatin capsule of size ‘0’ with white opaque body and dark blue opaque cap having ‘FCZ 200’ printed on body and cap in black linear pattern.

PRESENTATION:

CIPLA-FLUCONAZOLE 50 Capsules:	Carton containing transparent PVC and aluminium foil blister pack of 14 capsules.
CIPLA-FLUCONAZOLE 150 Capsules:	Carton containing transparent PVC and aluminium foil blister pack of 1 or 4 capsules.
CIPLA-FLUCONAZOLE 200 Capsules:	Carton containing transparent PVC and aluminium foil blister pack of 28 or 30 capsules.

STORAGE INSTRUCTIONS:

Store at or below 25°C, in a dry place.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

CIPLA-FLUCONAZOLE 50:	38/20.2.2/0098
CIPLA-FLUCONAZOLE 150:	38/20.2.2/0099
CIPLA-FLUCONAZOLE 200:	38/20.2.2/0100

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE

CERTIFICATE OF REGISTRATION:

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