**SCHEDULING STATUS:**

**S2**

**PROPRIETARY NAME AND DOSAGE FORM:**

**FLUCONAZOLE 150 GDC (capsule)**

**COMPOSITION:**

FLUCONAZOLE 150 GDC: Each capsule contains 150 mg Fluconazole

Contains sugar: Lactose 112 mg/capsule.

**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:**

**Fluconazole GDC 150** is indicated for the treatment of the following conditions in adults:

- Vaginal candidiasis - recurrent infections.

**CONTRA-INDICATIONS:**

- Hypersensitivity to **Fluconazole GDC 150**, other azole antifungal agents or to any of the excipients.
- Co-administration of terfenadine in patients receiving multiple doses of **Fluconazole GDC 150** in doses of 400 mg per day or greater (see INTERACTIONS).
- Co-administration of cisapride (see INTERACTIONS).
- Pregnancy and lactation (see PREGNANCY AND LACTATION).
- Multiple dose therapy is contra-indicated in patients with renal impairment.
- Concurrent use with astemizole should be avoided.

**WARNINGS:**

**Fluconazole GDC 150** 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 **Fluconazole GDC 150** therapy should be monitored for the development of more serious hepatic injury. **Fluconazole GDC 150** should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to **Fluconazole GDC 150**.

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 **Fluconazole GDC 150**. 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 **Fluconazole GDC 150** discontinued if bullous lesions or erythema multiforme develop.

**INTERACTIONS:**

**Fluconazole GDC 150** 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 **Fluconazole GDC 150** and medicines metabolised by cytochrome P450 can result in increased serum concentrations of the medicines metabolised by the same enzyme system.

**Fluconazole GDC 150** 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 **Fluconazole GDC 150** and concurrent use should be avoided (see CONTRAINDICATIONS).
- Cisapride - the concomitant administration of **Fluconazole GDC 150** 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 **Fluconazole GDC 150**.
- Midazolam and triazolam - **Fluconazole GDC 150** increases the serum concentrations of midazolam and triazolam and their psychomotor effects. 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 **Fluconazole GDC 150**. Patients on this combination need to have serum concentrations of tacrolimus monitored and dose reduction is necessary.

The following medicine increases plasma concentrations of **Fluconazole GDC 150** when given concomitantly:

- Hydrochlorothiazide

The following medicine decreases plasma concentrations of **Fluconazole GDC 150** when given concomitantly:

- Rifampicin - increased metabolism of **Fluconazole GDC 150** resulting in lower plasma concentrations of **Fluconazole GDC 150**.

**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 **Fluconazole GDC 150** are given concomitantly and patients should be monitored closely.

**PREGNANCY AND LACTATION:**

The use of **Fluconazole GDC 150** during pregnancy has resulted in congenital malformations and should be avoided. (see CONTRAINDICATIONS).

**Fluconazole GDC 150** should not be given to breast-feeding women. (see CONTRAINDICATIONS)

**Fluconazole GDC 150** is distributed into the breast milk at concentrations similar to those in plasma.

**DOSAGE AND DIRECTIONS FOR USE:**

Recurrent vaginal candidiasis

*Adults:* 150 mg administered as a single dose, once a month.

**Dosage in renal failure**

**Fluconazole GDC 150** should be used with caution in patients with impaired renal function. **Fluconazole GDC 150** 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 **Fluconazole GDC 150** after each dialysis session.

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

$$\text{Ccr male} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times (\text{plasma creatinine (micromole/litre)} \times \frac{1}{88})}$$

Ccr female - 0,85 x males

The pharmacokinetics of **Fluconazole GDC 150** 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 **Fluconazole GDC 150** 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:**

Very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000)

*Haematological System*

The following side effects have been reported and frequencies are unknown:

Leucopenia, neutropenia, agranulocytosis and thrombocytopenia

*Central and Peripheral Nervous system*

Very common - headache

The following side effects have been reported and frequencies are unknown:

Dizziness, vertigo, seizures, insomnia, nervousness, fatigue, rigors, malaise, hyperkinesia

*Endocrine / Metabolic*

The following side effects have been reported and frequencies are unknown:

Hypokalaemia, hypercholesterolaemia, hypertriglyceridaemia

*Gastrointestinal effects*

Very common - nausea, vomiting, abdominal pain, diarrhoea, flatulence

The following side effects have been reported and frequencies are unknown:

Taste perversion, dyspepsia, thirst

*Kidney / Genitourinary*

The following side effects have been reported and frequencies are unknown:

Female sexual dysfunction, intermenstrual bleeding, menorrhagia, leukorrhea, polyuria

*Liver effects*

Very common - hepatotoxicity (including elevated serum concentrations of alkaline phosphatase, bilirubin, ALT and AST)

The following side effects have been reported and frequencies are unknown:

Hepatic failure, hepatitis, hepatocellular necrosis, jaundice

*Musculoskeletal*

The following side effects have been reported and frequencies are unknown:

Hypertonia

*Ocular Effect*

The following side effects have been reported and frequencies are unknown:

Abnormal vision

*Skin/Dermatological Effects*

Very common - rash

Skin reactions are rare but exfoliative cutaneous reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome has been reported, more commonly in patients with AIDS.

The following side effects have been reported and frequencies are unknown:

Alopecia, urticaria, dry skin, abnormal odour

*Other*

The following side effects have been reported and frequencies are unknown:

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

**Special Precautions**

Liver function should be monitored periodically in all patients receiving continuous treatment with **Fluconazole GDC 150** for more than one month or when a patient develops signs or symptoms suggestive of liver dysfunction. **Fluconazole GDC 150** should be discontinued if abnormalities in enzyme values persist, worsen or if they are accompanied by symptoms of hepatotoxicicty. **Fluconazole GDC 150** 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 over dose: The following have been reported with an overdose of **Fluconazole GDC**:

insomnia, irritability, vomiting, diarrhea, abdominal pain/ cramps, anorexia, bulging fontanel, elevation of alkaline phosphates and gamma glutamyl transpeptidases, increase in serum calcium, renal failure, fatigue, facial rash, skin erythema, generalized urticaria, arthralgia. Itching, numbness of the tongue and depressed mood.

Treatment of overdose: Treatment is symptomatic and supportive. There is no specific antidote.

**Fluconazole GDC 150** is largely excreted in the urine. Forced diuresis may increase the elimination rate. Elimination of **Fluconazole GDC 150** can be facilitated by haemodialysis. The concentration of **Fluconazole GDC 150** can be decreased by about 50 % by a three hour haemodialysis session.

**IDENTIFICATION:**

Size 1 hard gelatin capsule with a blue cap and a blue body.

**PRESENTATION:**

PVC/Aluminium blister pack containing 1 capsule packed into a unit carton of 1 capsule.

**STORAGE INSTRUCTIONS:**

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

Do not remove capsules from unit carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBER:**

41/20.2.2/0124

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

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