1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. NAME OF THE MEDICINAL PRODUCT

FLUCAMIL 50 mg Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:
Fluconazole USP…….. 50 mg.
Excipients…….… Q.S.
Approved colors used in empty capsule shell

3. PHARMACEUTICAL FORM

Capsule
For oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaginal candidiasis, acute or recurrent and prophylaxis to reduce the incidence of recurrent vaginal candidiasis.
Candidial balanitis
Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea unguium (onychomycosis), and dermal candida infections.

4.2 Posology and method of administration

Adults
For oropharyngeal candidiasis, the usual dose is 50 to 100mg once daily for 7-14 days. In patients with severely compromised immune function, treatment can be continued for longer periods if necessary.
For Chronic mucocutaneous candidiasis, the dose is 50 mg to 100 mg daily Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromisation and infection.
For dermatomycosis, the dose is 50 mg once daily for 2 to 4 weeks.

Children
For the treatment of oropharyngeal candidiasis in children, the recommended fluconazole dosage is 6 mg/kg on the first day, followed by 3 mg/kg once daily. To lower the likelihood of relapse, treatment should be administered for at least 2 weeks.

Method of administration: Oral

4.3 Contraindications

Fluconazole should not be used in patients with known sensitivity to the medicine or to related triazole compounds.

Concomitant administration of terfenadine is contra-indicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Co-administration of cisapride is contra-indicated in patients receiving Fluconazole.
Multiple-dose therapy should be carefully monitored in patients with renal impairment. Safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

If a rash develops which is considered attributable to Fluconazole, further therapy with this agent should be avoided.
Geriatrics:
No geriatrics-specific problems have been documented with the use of Fluconazole.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants: Fluconazole has been shown to prolong prothrombin times in subjects receiving warfarin. **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.
Oral hypoglycemics: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas.
Cyclosporin: A kinetic study in renal transplant patients found fluconazole 200 mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100 mg daily, fluconazole did not affect cyclosprin levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.
Hydrochlorothiazide: Co-administration of multiple doses of hydrochlorothiazide may increase the plasma concentrations of fluconazole.
Phenytoin: Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinically significant degree.

4.6 Pregnancy and lactation

Pregnancy :
An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.
There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Breast-feeding :
Fluconazole passes into breast milk to reach concentrations similar to those in plasma. Breast-feeding may be maintained after a single dose of 150mg fluconazole. Breast-feeding is not recommended after repeated use or after high dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need

for Fluconazole capsules and any potential adverse effects on the breast-fed child from Fluconazole capsules or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Fluconazole capsule on the ability to drive or use machines.

4.8 Undesirable effects

Central and Peripheral Nervous System: Dizziness, seizures, hyperkinesia, hypertonia, vertigo.
Dermatologic: Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Gastro-intestinal: Dyspepsia
Haematopoetic and Lymphatic: Leucopenia including neutropenia and agranulocytosis, thrombocytopenia.
Immunologic: Anaphylaxis (including angioedema , face oedema, pruritis).
Liver/Biliary: Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.
Metabolic/Nutritional: Hypercholesterolemia, hypertriglyceridemia, hypokalemia, thirst, polyuria.
Psychiatric: Insomnia, nervousness.
Reproductive: Female sexual dysfunction, intermenstrual bleeding, leukorrhoea and menorrhagia.
Body as a whole: Fatigue, malaise, rigors, flushing.
Other senses: Taste perversion, abnormal vision.

4.9 Overdose

There have been reports of overdose with Flucamil and hallucination and paranoid behaviour have been concomitantly reported.
In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.
Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemodialysis session decreases plasma levels by approximately 50%.

5.PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for SystemicUse (Triazole derivatives)
ATC-CODE: JO2AC01

Mechanism of action
Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for

fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.
Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

5.2 Pharmacokinetic properties

Absorption
After oral administration fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.
Distribution
The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).
Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.
Biotransformation
Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a moderate inhibitor of the isozymes CYP2C9 and CYP3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19.
Excretion
Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.
Carcinogenesis
Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 27 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.
Mutagenesis
Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of Salmonella typhimurium, and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000 μg/ml) showed no evidence of chromosomal mutations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch	BP
Di-basic calcium phosphate	BP
Soluble starch	IHS
Purified talc	BP
Sdium lauryl sulphate	BP
Colloidal anhydrous silica	BP
Green/ Yellow colored FML-50 printed size "2" capsule	IHS

6.2 Incompatibilities

NA

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Store below 30°C protected from moisture.
KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

1 x 3 Alu-PVC Blister pack in a printed carton along with package insert.
1 x 10 Alu-Alu Blister pack in a printed carton along with package insert.

6.6 Special precautions for disposal and other handling

Not Applicable.

7. MANUFACTURER

saga LABORATORIES
Ahmedabad 382 210
Gujarat, India.
E-mail: info@sagalabs.com
URL: www.sagalabs.com