SUMMARY OF PRODUCT CHARCETERSTICS

ETHIZOLE Capsules 150mg

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Ethizole 150 mg Capsules.
Fluconazole 150 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Fluconazole 150 mg.

3. PHARMACEUTICAL FORM

A white powder filled in size '2' hard gelatin capsules having turquoise blue cap and body

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ethizole 150 is indicated for the treatment of the following conditions:-
Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balanitis. The treatment of partners who present with symptomatic genital candidiasis should be considered.

4.2 Posology and method of administration

For oral use.
***In Adults*:**
Vaginal candidiasis or candidal balanitis – 150mg single oral dose.
In Children:
Despite extensive data supporting the use of fluconazole in children there are limited data available on the use of fluconazole for genital candidiasis in children below 16 years. Use at present is not recommended unless antifungal treatment is imperative and no suitable alternative agent exists.
Use in the Elderly:
The normal adult dose should be used.
Use in renal impairment:
Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required.

4.3 Contraindications

Fluconazole should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or to any of the other ingredients.

Co-administration of terfenadine or cisapride is contraindicated in patients receiving fluconazole. (See "Interactions with other medicinal products and other forms of

interaction").

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use with caution in patients with renal impairment. (See "Use in patients with impaired renal function" in Section 4.2).

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in haematological, hepatic, renal and other biochemical function test results have been observed during treatment with fluconazole but the clinical significance and relationship to treatment is uncertain.

Very rarely, patients who died with severe underlying disease and who had received multiple doses of fluconazole had post-mortem findings which included hepatic necrosis. These patients were receiving multiple concomitant medications, some known to be potentially hepatotoxic, and/or had underlying diseases which could have caused the hepatic necrosis.

In cases of hepatotoxicity, no obvious relationship to total daily dose of fluconazole, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of fluconazole therapy.

As a causal relationship with fluconazole cannot be excluded, patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with fluconazole.

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many drugs. If a rash develops in a patient treated for a superficial fungal infection which is considered attributable to fluconazole, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.
In rare cases, as with other azoles, anaphylaxis has been reported.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin
Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in

the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase in the fluconazole dose should be considered.

Hydrochlorothiazide

In a kinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.

Anticoagulants

In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. As with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melaena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored.

Benzodiazepines (Short acting)

Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and 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 is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patients should be appropriately monitored.

Sulphonylureas

Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind.

Phenytoin

Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinically significant degree. If it is necessary to administer both drugs concomitantly, phenytoin levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels.

Oral contraceptives

Two kinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in a 50mg fluconazole study, while at 200mg daily the AUCs of ethinyloestradiol and levonorgestrel were increased 40% and 24% respectively. Thus multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Endogenous steroid

Fluconazole 50mg daily does not affect endogenous steroid levels in females: 200 – 400mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

Ciclosporin

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

Theophylline

In a placebo controlled interaction study, the administration of fluconazole 200mg for 14 days resulted in an 18% decrease in the mean plasma clearance of theophylline. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and the therapy modified appropriately if signs of toxicity develop.

Terfenadine

Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness, and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole. (See "Contra-indications").

Cisapride

There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illnesses, and the relationship of the reported events to a possible fluconazole-cisapride drug interaction is unclear. Because of the potential seriousness of such an interaction, co-administration of cisapride is contra-indicated in patients receiving fluconazole. (See "Contra-indications").

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 200mg 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 infected patients. On two occasions, 21 days apart, patients received zidovudine 200mg every eight hours either with or without fluconazole 400mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co- administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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 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 fluconazole and tacrolimus were co-administered. Pateints receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

The use of fluconazole in patients concurrently taking astemizole or other drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.

Interaction studies have shown that when oral fluconazole is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but that such interactions may occur.

4.6 Pregnancy and lactation

Use during pregnancy

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear.

Accordingly, fluconazole should not be used in pregnancy or in women of childbearing potential unless adequate contraception is employed. Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the foetus.

Use during lactation

Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

4.7 Effects on ability to drive and use machines

Experience with fluconazole indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

4.8 Undesirable effects

The following treatment–related undesirable effects were reported in 4,048 patients receiving fluconazole for 7 or more days in clinical trials:

Organ systems	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
General			fatigue, malaise, asthenia, fever		
Central and Peripheral Nervous System		Headache	Convulsions, dizziness, Paraesthesia, tremor, vertigo		
Skin and Appendages		Skin Rash	Pruritus	Exfoliative Skin disorder (Stevens-Johnson Syndrome)	
Gastrointestinal		Nausea and Vomiting, abdominal pain, diarrhoea	Anorexia, constipation, dyspepsia, flatulence		
Musculoskeletal			Myalgia		
Autonomic Nervous System			Dry mouth, increased sweating		
Psychiatric			Insomnia, somnolence		
Liver and Biliary System		Clinically significant increase of AST, ALT and alkaline	Cholestasis, hepatocellular damage, jaundice. Clinically	Hepatic Necrosis	

		phosphatase	significant increase o total bilirubin		
Special Senses			Taste perversion		
Hematopoietic and Lymphatic			Anaemia		
Immunologic				Anaphylaxis	

Adverse clinical events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post-marketing experience):

Organ Systems	Very Common >1/10	Common > 1/100, < 1/10	Uncommon > 1/1,000, < 1/1,00	Rare > 1/10,000, < 1/1,000	Very rare < 1/10,000
Central and Peripheral Nervous System				Seizures	
Skin and Appendages				Alopecia	Exfoliative skin disorder (Stevens-Johnson Syndrome and toxic epidermal necrolysis), erythema

					exudativum multiforme
Liver and Biliary system				Hepatic Failure,hepatitis, hepatic necrosis	
Immunologic					Anaphylaxis, angiodema, face oedema and pruritus
Hematopoietic and Lymphatic				Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia	
Metabolic				Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia	

4.9 Overdose

There have been reports of overdosage with fluconazole and in one case, a 42 year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200mg of fluconazole, unverified by his physician. The patient was admitted to the hospital and his condition resolved within 48 hours.

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

As 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

5.1 Pharmacodynamic properties

J02A C01 Antimycotics for systemic use – triazole derivatives Fluconazole, a member of the triazole class of antifungal agents, is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol.

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbital sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

There have been reports of cases of superinfection with Candida species other than C. albicans, which are often inherently not susceptible to fluconazole (e.g. Candida krusei). Such cases may require alternative antifungal therapy.

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole 50mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200-400mg 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 50mg do not affect its metabolism.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. 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 with a plasma elimination half-life of approximately 30 hours. 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. 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% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentration was still 5.8 microgram/g.

The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

The long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis and once daily dosing for other indications.

5.3 Preclinical safety data

Reproductive Toxicity:
Increases in fetal anatomical variants (supernumary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60x the recommended human dose) to 320mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification.

Carcinogenesis:
Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10mg/kg/day. Male rats treated with 5 and 10mg/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 S.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 1000µg/ml) showed no evidence of chromosomal mutations.

Impairment of Fertility:
Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Lactose
Magnesium stearate
Colloidal anhydrous silica
HEG SZ 2 Torquoise blue B/C

6.2 Incompatibilities

No specific incompatibilities have been noted.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Tablets in Alu-PVC blister pack. Pack size is 1's and 10's blister.

6.6 Special precautions for disposal and other handling

Not applicable.

7. APPLICANT/MANUFACTURER

SK Medicines Ltd.,
Nigeria.

Manufacturer:
Medreich Limited
Survey No: 11, 12, 13, 14, & 15, Poojaramanahalli Village,
Hoskote Taluk, Bengaluru, 562 114,
Karnataka, India.