Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ByFluc 200 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluconazole 200 mg.

Each capsule also contains lactose monohydrate 188mg and azorubine (E122)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules.

Purple opaque cap and white opaque body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

ByFluc 200mg Capsules is indicated for:

1. Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balanitis.

2. Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated.

3. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium and pulmonary and urinary tracts. Candidal infections in patients with malignancy, in intensive care units or those receiving cytotoxic or immunosuppressive therapy, may be treated.

4. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts and patients with acquired immune deficiency syndrome (AIDS), organ transplants or other causes of immunosuppression may be treated. ByFluc 200mg Capsules can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

5. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy or radiotherapy, including bone marrow transplant patients.

6. Dermatomycoses including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and candida infections, only where these conditions are resistant to first line therapy or where occurrence is in immunocompromised patients.

4.2 Posology and method of administration

ByFluc 200mg Capsules should be administered orally.

The daily dose of ByFluc 200mg Capsules should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy.

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 usually require maintenance therapy to prevent relapse.

Adults:

1. Candidal vaginitis or balanitis. The usual dosage is 150 mg as a single dose.

2. Mucosal Candidiasis

Oropharyngeal candidiasis: the recommended dose is 50mg once daily for 7 to 14 days. Treatment may continue for a longer period if the physician so requires.

Atropic oral candidiasis associated with dentures: the recommended dose is 50mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.

For other candidal infections of the mucosa, (except genital candidiasis see above), e.g. oesophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutaneous candidiasis etc., the recommended dose is 50mg daily, given for 14 to 30 days. In unusually difficult cases of mucosal candidal infections the dose may be increased to 100mg daily.

3. For candidaemia, disseminated candidiasis and other invasive candidal infections: the recommended dose is 400mg on the first day followed by 200mg once daily. Depending on the clinical response the dose may be increased to 400mg once daily. Duration of treatment is based upon the clinical response.

4a. For cryptococcal meningitis and cryptococcal infections at other sites: the recommended dose is 400mg on the first day followed by 200mg - 400mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6 to 8 weeks for cryptococcal meningitis.

4b. For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, ByFluc 200mg Capsules may be administered indefinitely at a daily dose of 100 - 200 mg.

5. The recommended dosage for the prevention of candidiasis is 50 to 400 mg once daily, based on the patient's risk of developing fungal infection. For patients at high risk of systemic infection e.g. patients who are anticipated to have profound or prolonged neutropenia such as during bone marrow transplantation, the recommended dose is 400mg once daily. ByFluc 200mg Capsules 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.

6. For dermal infections including tinea pedis, corporis, cruris and candida infections the recommended dosage is 150mg once weekly or 50mg once daily. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks. For tinea versicolor the recommended dose is 50mg once daily for 2 to 4 weeks.

Use in children:

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. The maximum adult dosage should not be exceeded in children. ByFluc 200mg Capsules is administered as a single daily dose each day.

For children with impaired renal function the daily dose should be reduced in accordance with the guidelines given for adults, dependent on the degree of renal impairment.

Use in the elderly:
The normal dose should be used if there is no evidence of renal impairment. In patients with renal impairment (creatinine clearance less than 50ml/min) the dosage schedule should be adjusted as described below.

Use in renal impairment:
Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required. In patients with impaired renal function who will receive multiple doses of ByFluc 200mg Capsules, the normal recommended dose (according to indication) should be given on day 1, followed by a daily dose based on the following table:

Creatinine clearance (ml/min)	Percent of recommended dose
>50	100%
11-50	50%
Patients receiving regular dialysis	One dose after every dialysis session

4.3 Contraindications

ByFluc 200mg Capsules should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds.

Co-administration of terfenadine is contra-indicated in patients receiving ByFluc 200mg Capsules at multiple doses of 400mg per day or higher based upon results of a multiple dose interaction study.

Co-administration of cisapride is contra-indicated in patients receiving ByFluc 200mg Capsules. (see "Interaction with other medicinal products and other forms of interaction")

4.4 Special warnings and precautions for use

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities of hepatic, renal, haematological and other biochemical function tests have been observed during treatment with ByFluc 200mg Capsules but the clinical significance and relationship to treatment is uncertain.

ByFluc 200mg Capsules has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of ByFluc 200mg Capsules-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. ByFluc 200mg Capsules hepatotoxicity has usually been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during ByFluc 200mg Capsules therapy should be monitored for the development of more serious hepatic injury. ByFluc 200mg Capsules should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to ByFluc 200mg Capsules.

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 ByFluc 200mg Capsules, further therapy with this agent should be discontinued. In patients with invasive/systemic fungal infections who develop rashes, they should be monitored closely and ByFluc 200mg Capsules discontinued if bullous lesions or erythema multiforme develop.

There is little information on safety in long-term use.

In rare cases, as with other azoles, anaphylaxis has been reported.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose

malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants: In an interaction study, fluconazole increased the prothrombin time after warfarin administration in healthy males. Though the magnitude of change was small (12%), careful monitoring of prothrombin time in patients receiving coumarin-type anticoagulants is recommended.

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.

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.

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.

Rifampicin: Concomitant administration of fluconazole and rifampicin has 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.

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 the 50mg fluconazole study, while at 200mg daily the AUCs of ethinyl estradiol 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.

Cyclosporin: A kinetic study in renal transplant patients found Fluconazole 200mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100mg daily, fluconazole did not affect cyclosporin levels in patients with bone marrow transplants. Cyclosporin 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 cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction 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 doses of 400mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400mg or greater with terfenadine is contraindicated. (See “Contraindications”.) The co-administration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully

monitored.

Cisapride: There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were co-administered. A controlled study found that concomitant fluconazole 200mg once daily and cisapride 20mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Co-administration of cisapride is contraindicated in patients receiving fluconazole.

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.

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 coadministration with Fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

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.

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.

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 Fertility, 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 use and these events is unclear**.**

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 ByFluc 200mg Capsules indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

4.8 Undesirable effects

Fluconazole is generally well tolerated. The most common undesirable effects observed during clinical trials and associated with fluconazole are:

Central and Peripheral Nervous System Headache.

Skin/Appendages Rash.

Gastrointestinal Abdominal pain, diarrhoea, flatulence, nausea.
In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain (see Section 4.4 "Special warnings and precautions for use").

Liver/Biliary Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

In addition, the following undesirable effects have occurred during post-marketing:

Central and Peripheral Nervous System Dizziness, seizures.

Skin/Appendages Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Gastrointestinal Dyspepsia, vomiting.

Haematopoietic and Lymphatic Leucopenia including neutropenia and agranulocytosis, thrombocytopenia.

Body As A Whole Anaphylaxis (including angioedema, face oedema, pruritis, urticaria).

Liver/Biliary Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Other senses Taste perversion.

4.9 Overdose

There has been a reported case of overdosage with fluconazole. A 42 year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200mg of fluconazole. The patient was admitted to the hospital and his condition was 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

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 pentobarbitone 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.

Both orally and intravenously administered fluconazole was active in a variety of animal fungal infection models. Activity has been demonstrated against opportunistic mycoses, such as infections with *Candida* spp. including systemic candidiasis in immunocompromised animals; with *Cryptococcus neoformans*, including intracranial infections; with *Microsporum* spp. and with *Trichophyton* spp. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitides*; with *Coccidioides immitis*, including intracranial infection and with *Histoplasma capsulatum* in normal and immunosuppressed animals.

There have been reports of cases of super-infection 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.

5.2 Pharmacokinetic properties

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.

In children, the following pharmacokinetic data have been reported:

Age studied	**Dose (mg/kg)**	**Half-life (hours)**	**AUC (microgram/h/ml)**
11 days - 11 months	Single-IV 3mg/kg	23	110.1
9 months - 13 years	Single-Oral 2mg/kg	25.0	94.7
9 months - 13 years	Single-Oral 8mg/kg	19.5	362.5
5 years - 15 years	Multiple-IV 2mg/kg	17.4*	67.4
5 years - 15 years	Multiple-IV 4mg/kg	15.2*	139.1
5 years - 15 years	Multiple-IV 8mg/kg	17.6*	196.7
Mean Age 7 Years	Multiple-Oral 3mg/kg	15.5	41.6

*Denotes final day

In premature new-borns (gestational age around 28 weeks), intravenous administration of fluconazole of 6mg/kg was given every third day for a maximum of five doses while the premature new-borns remained in the intensive care unit.

The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13.

The area under the curve (microgram/h/ml) was 271 (range 173-385) on day 1 which increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13.

The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased with time to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in Elderly
A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 mcg/ml and occurred at 1.3 hours post dose. The mean AUC was 76.4 ± 20.3 mcg/h/ml, and the mean terminal half-life was 46.2 hours.

These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Co-administration of diuretics did not significantly alter AUC or C_{max}. In addition, creatinine clearance (74 ml/min), the percent of drug recovered unchanged in urine (0-24 hr, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristic of this group. A plot of each subject's terminal elimination half-life versus creatinine clearance compared with the predicted half-life – creatinine clearance curve derived from normal subjects and subjects with varying degrees of renal insufficiency indicated that 21 of 22 subjects fell within the 95% confidence limit of the predicted half-life – creatinine clearance curves. These results are consistent with the hypothesis that higher values for the pharmacokinetic observed in the elderly subjects compared with normal young male volunteers are due to the decreased kidney function that is expected in the elderly.

5.3 Preclinical safety data

Reproductive Toxicity: There were no fetal effects at 5 or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. Theses effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

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. 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 *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 1000 µg/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 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/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

Lactose monohydrate
Maize starch
Colloidal anhydrous silica
Magnesium stearate
Sodium laurilsulfate.
The capsule shells contain gelatin, titanium dioxide (E171), azorubine (E122) and brilliant blue FCF (E133).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Byfluc 200 mg capsules are supplied in PVC/PVdC-aluminium blisters within cardboard cartons.
The packs contain 1, 7, 10, 20, 30, 50, or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Helsinn Birex Therapeutics Ltd
Damastown
Mulhuddart
Dublin 15

8 MARKETING AUTHORISATION NUMBER

PA 915/28/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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