Stabilanol®

FLUCONAZOLE

PATIENT INFORMATION LEAFLET

1. DESCRIPTION OF MEDICINAL PRODUCT

1.1 NAME: Stabilanol

1.2 COMPOSITION: Active substance: Fluconazole.

•**50mg/cap: Excipients:** Lactose monohydrate, cellulose microcrystalline, starch maize pregelatinized, silicon dioxide colloidal, magnesium stearate, sodium lauryl sulfate. **Composition of empty capsule:** Iron oxide (yellow) E 172, Patent blue V E131, Titanium dioxide E171, quinoline yellow E104, Gelatin.

•**100mg/cap: Excipients:** Lactose monohydrate, cellulose microcrystalline, starch maize pregelatinized, silicon dioxide colloidal, magnesium stearate, sodium lauryl sulfate. **Composition of empty capsule:** Iron oxide (yellow) E 172, Titanium dioxide E171, Gelatin

•**150mg/cap: Excipients:** Lactose monohydrate, cellulose microcrystalline, starch maize pregelatinized, silicon dioxide colloidal, magnesium stearate, sodium lauryl sulfate. **Composition of empty capsule:** Titanium dioxide E 171, Quinoline yellow E 104, Sunset yellow FCF E 110 (orange yellow), Gelatin.

•**100mg/50ml (Vial): Excipients:** Sodium chloride, water for injection.

1.3 PHARMACEUTICAL FORM:

Capsules, Solution for intravenous infusion.

1.4 STRENGTH OF ACTIVE SUBSTANCE:

•**Capsules:** 50mg, 100mg, 150mg

•**Solution for intravenous infusion:** 100mg/50ml (Vial)

1.5 DESCRIPTION - PACKAGE

•**Capsules 50mg:** Cardboard pack containing 7 capsules in transparent PVC/ Aluminium blister with patient information leaflet.

•**Capsules 100mg:** a) Cardboard pack containing 7 capsules in transparent PVC/ Aluminium blister with instructions on usage b) Cardboard pack containing 14 capsules placed in 2 transparent PVC/ Aluminium blisters with patient information leaflet.

•**Capsules 150mg:** Cardboard pack containing 1 capsule in transparent PVC/ Aluminium blister with patient information leaflet.

•**Solution for intravenous infusion:** Cardboard pack containing a transparent glass vial of 50ml sealed with a rubber stopper and aluminum cap; with patient information leaflet.

1.6 THERAPEUTIC CATEGORY:

Antifungal agent.

1.7 MARKETING AUTHORIZATION HOLDER / MANUFACTURER:

PHARMATHEN S.A., 6, DERVENAKION STR., 153 51 PALLINI ATTIKIS, TEL.: +30.210.6665067

2. INFORMATION REGARDING THE MEDICINE PRESCRIBED FOR YOU BY YOUR DOCTOR

2.1 GENERAL INFORMATION:

Fluconazole belongs to a group of medicines called the triazole antifungal agents and is a potent and specifc inhibitor of sterol synthesis in fungi.

2.2 INDICATIONS

Systemic mycoses:

1. Cryptococcal infections including cryptococcal meningitis and infections of other areas (e.g. lungs, skin). AIDS patients, as well as patients who have undergone an organ transplant or present other causes of immunosuppression may be treated. Fluconazole may be used for the prevention of recurrent cryptococcal diseases in AIDS patients.
2. Generalized candidiasis including candidaemia in clinically stable and non-neutropenic patients, diffused and metastatic candidiasis (infections of the peritoneum, endocardium, as well as lung and urinary tract infections). Patients with malignant neoplasms or in intensive care units, as well as patients receiving cytostatic or immunosuppressive drugs or patients presenting other factors in favor of candidiasis may also be treated with the drug. It is self-evident that for indications 1 and 2, cultures and proper laboratory examinations should be conducted before the initiation of the treatment (immediate microscopic examination, biopsies, serum examinations), in order to isolate and identify the causative factor.
3. Deep endemic mycoses, such as coccidioidomycosis, paracoccidioidomycosis, sporotrichosis and histoplasmosis in immunocompetent patients.
4. Mucosal candidiasis. This includes oropharyngeal and oesophageal candidiasis (as an alternative to topical treatment), non-invasive bronchopulmonary candidiasis. Candiduria, chronic mucocutaneous candidiasis. Chronic atrophic oral candidiasis (stomatitis due to dentures), as alternative to local treatment. Patients mostly with immune system disorders can undergo a treatment with the drug.
5. Genital candidiasis:
   Vaginal candidiasis as an alternative to topical treatment (only as one single dose of 150mg)
   a) acute
   b) relapsing as long as the infection has been confirmed by culture (usually of non-inflammatory cause but due to allergy or hypersensitivity).
   Candidal balanitis.
6. Dermatophytoses including infections of the foot, of the thin skin layer and of the bikini line, as well as tinea versicolor, onychomycosis and infections caused by CANDIDA.
   Note: Systemic treatment in the case of the indications mentioned above is preferable when the infection extends to a large skin area or the scalp, or in patients with disorders of defense mechanisms, unresponsive to local treatment and persistence of the mycotic infection despite treatment.
7. Prevention of candidiasis in patients with neutropenia and malignant diseases that predispose to the development of such infections as a result of chemotherapy with cytostatic drugs or radiotherapy in cases of marrow transplant. Caution: chronic administration of azoles increases the possibility of development of C. KRUSEI, ASPERGILLUS, MUCORALES, FUSARIUM, T. GLABRATA that usually present a natural resistance to azoles.

Therapy may be initiated before the results of the cultures and other laboratory studies are known. However when the results are known, therapy should be adjusted accordingly.

2.3 Contra-indications:

Stabilanol should not be administered in patients with known sensitivity to Fluconazole or to the excipients or to related azole preparations. Co-administration of cisapride is contra-indicated in patients receiving fluconazole. Based on the results of a multiple dose interaction study, co-administration of terfenadine in patients receiving fluconazole at doses of 400 mg or more per day is contraindicated.

2.4 Special warnings and special precautions for use:

2.4.1 General:

Hepatic failure: the administration of fluconazole has been correlated in rare cases to severe hepatotoxicity which in exceptional cases has led to fatality, especially in patients with severe illness.In patients taking fluconazole and with the appearance of hepatotoxicity, no correlation with the total daily dose, the duration of the therapy, gender or age was observed. Hepatotoxicity from fluconazole is usually, but not always, reversible, after treatment discontinuation.

Patients with biochemical disturbances of hepatic function throughout the duration of treatment with fluconazole, must be closely monitored for the possibility of developing severe hepatic failure. Fluconazole should be discontinued if clinical signs and symptoms of hepatic disease are observed.

Rarely, patients have developed exfoliative cutaneous reactions such as Stevens-Johnson syndrome or a bullous epidermal necrolysis erythema during treatment with fluconazole. Patients with AIDS are more prone to the development of severe cutaneous reactions with many drugs. If a rash develops in patients treated for superfcial fungal infections which is considered attributable to fluconazole, therapy should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and treatment with fluconazole should be discontinued if bullous lesions or erythema multiforme develop.

In rare cases, anaphylaxis has been reported.

2.4.2 Administration in the elderly:

If there are no indication of renal function impairment, the usual dose of the drug should be administered. In patients with renal dysfunction (creatinine clearance <50 ml/min) the dosage regimen should be adjusted as described in paragraph 2.6 "Posology and method of administration".

2.4.3 Use in pregnancy:

Fluconazole administration in pregnancy should be avoided, except in the case of patients with severe and life threatening fungal infections, in which the drug can be administered if the expected benefts from the treatment outweigh potential risks of toxic effects on the foetus.

2.4.4 Use in breast feeding:

Fluconazole administration in breast feeding mothers is not recommended.

2.4.5 Use in children:

See Posology

2.4.6 Effects on ability to drive and use machines:

Fluconazole does not impair a patient's ability to drive or use machinery.

2.4.7 Special warnings for the included excipients:

Stabilanol capsules contain lactose.

This may make them unsuitable for people with lactase insuffciency, galactosaemia or glucose/galactose malabsorption syndrome. These conditions affect the way people metabolize lactose. Your doctor may have told you if you have these conditions.

2.5 Drug Interactions:

Fluconazole may interact with other drugs such as anticoagulants, sulfonylureas, hydrochlorothiazine, phenytoin, oral contraceptives, rifampicin, cyclosporin, theophylline, terfenadine, zidovudine and astemizole If you receiving any of these drugs, consult your doctor. Co-administration with cisapride is not recommended.

2.6 Posology and method of administration:

As absorption of orally administered Fluconazole is rapid and complete, the Fluconazole daily dose is the same for both oral and intravenous administration.

The Fluconazole daily dose should be based on the type and severity of the mycotic infection. Most cases of vaginal candidiasis respond therapeutically to single dose administration.

For infections requiring multiple dose administration, treatment should be continued until the clinical parameters and laboratory examinations show resolution of the active mycotic infection. Insuffcient duration of Fluconazole treatment may result in a relapse of the active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require preventative treatment to reduce the occurrence of relapses.

Adults

1a. For the treatment of cryptococcal meningitis and cryptococcal infections of other body areas, the usual dose is 400mg on the frst day of the treatment followed by a dose of 200-400mg once daily. The duration of treatment in

cryptococcal infections depends on the clinical mycological response but usually lasts from 6 to 8 weeks in cryptococcal meningitis and 10 to 12 weeks after a negative result of the CSF culture.

1b. For the prevention of cryptococcal meningitis relapse in patients with AIDS, after the completion of the initial treatment it is possible to administer Fluconazole indefinitely at a daily dose of 100-200mg

2. For the treatment of candidaemia, generalized candidiasis and other severe candidiases, the usual dose is 400mg on the first day of the treatment, followed by a daily dose of 200mg. Depending on the clinical response of the patients, the dose may be increased to 400mg daily. The treatment's duration depends on the clinical response of the patients.
3. With regard to deep endemic mycosis, doses of 200-400mg daily for a duration of treatment which may last 2 years may prove to be necessary. Duration of treatment should be adapted in every case.
4. For the treatment of oropharyngeal candidiasis, the usual dose is 50-100mg once daily for 7-14 days. If necessary, the treatment may be continued for a longer time span in patients with a severe disorder of the immune system. For the treatment of atrophic oral candidiasis associated with artifcial dentures, the usual Fluconazole dose is 50mg once daily for 14 days, concurrently administered with the application of local antiseptic measures to the dentures.
   For the treatment of other candidiasis infections of the mucosa (except vaginal candidiasis, see below), e.g. oesophagitis, non-invasive bronchopulmonary infections, candidurea, chronic muco-cutaneous candidiasis etc., the usual Fluconazole dose is 50-100mg daily for 14-30 days.
5. For the treatment of vaginal candidiasis and candidal balanitis, 150mg of Fluconazole should be administered orally as a single dose.
6. For the treatment of skin infections including infections of the feet, of the thin skin layer and of the bikini line, as well as tinea versicolor and infections caused by Candida, the recommended dose is 150mg once weekly or 50mg once daily. The duration of treatment usually extends from 2 to 4 weeks but in particular infection of the feet may require treatment for up to 6 weeks. For tinea versicolor, the recommended dose is 50mg once daily for 2 to 4 weeks.
7. For onychomycosis, the recommended dose is 150mg once weekly. Treatment should be continued until the infected nail is replaced due to normal nail growth. Normally it takes about 3 to 6 months and 6 to 12 months respectively for fngernails and toenails to grow. Of course the growth rate may vary considerably from person to person and according to patient's age. After a successful long-term treatment of chronic infections, the nails may still show traces of infection.
8. For the prevention of fungal infections in patients with an increased risk of generalized infection e.g. patients who are expected to have severe or prolonged neutropenia, like pre-marrow transplant patients, the daily recommended dose of the drug should be 400mg and for the prevention of fungal infections in patients with neutropenia and malignant diseases who are predisposed to the development of such infections as a result of chemotherapy with cytostatic drugs of radiotherapy, the daily dose of the drug is 50-400mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count is above 1000 cells per mm^3.

Children older than 4 weeks

As with similar infections in adults, the duration of treatment is based on the clinical response. The maximum daily dosage in adults should not be exceeded in children. Fluconazole is administered as single dose each day only for the following indications:

The recommended dose for mucosal candidiasis is 3 mg/kg daily. A loading dose of 6 mg/kg may be used on the frst day to achieve steady state levels of serum concentration more rapidly.

For the treatment of generalized candidiasis and cryptococcal infections, the recommended dosage is 6 -12 mg/kg daily, depending on the severity of the disease.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 to 12 mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing).

In children with renal function impairment, the daily dose should be reduced according to the instructions provided for adults, depending on the degree of the renal impairment.

Neonates

In neonates, excretion of fluconazole is slow. In the frst two weeks of life, the same mg/kg dosing should be used for the same indications as in older children, but administered every 72 hours. During weeks 3-4 of life, the same dose should be given every 48 hours.

Patients with renal impairment

Fluconazole is largely eliminated in the urine in an unaltered form. In case of administration of a single, dose of the drug its adjustment is not necessary. When multiple doses are administered to patients with renal impairment, a loading dose of 50 to 400 mg is administered. After the loading dose, the daily dose (according to the indications) should be adjusted according the following table:

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

When serum creatinine is the only measurement of renal failure, the following equation for creatinine is applied:

Men: $\frac{\text{Body weight (kg) x (140 - age)}}{72 \times \text{serum creatinine (mg / 100ml)}}$

Women: 0.85 of the male value

Administration

Fluconazole may be administered either orally or by intravenous infusion at a rate which does not exceed 10 ml/minute. The route of administration depends on the clinical state of the patient. When converting from oral to intravenous route of administration, or vice versa, there is no need to change the daily dose of the drug. Fluconazole is presented in a 0.9% sodium chloride solution. Each 200 mg (vial of 100 ml) contains 15mmol Na^+ and Cl^-. As Fluconazole is presented in a dilute sodium chloride solution, the rate of fluid administration should be evaluated in patients requiring restriction of sodium or fluids.

2.7 Overdose:

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 increases the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

2.8 Undesirable effects:

Fluconazole is generally well tolerated.

The most common undesirable effects associated with the use of Fluconazole relate to the gastrointestinal system. They include nausea, abdominal discomfort, diarrhoea and flatulence. Other common undesirable effects are headache and skin rashes. Exfoliating dermatitis, such as the Stevens-Johnson syndrome and toxic epidermic necrolysis, especially in patients with AIDS receiving other drugs are rarely reported.

Disorders of renal function, the hematopoietic system function, and hepatic function have been reported (see warning) during treatment with Fluconazole and associated drugs in some patients particularly those with severe underlying diseases such as AIDS and cancer. As with other azoles, cases of anaphylaxis have been reported on rare occasions. Seizures, leucopenia, thrombocytopenia, hypercholesteraemia, hypertriglyceridaemia and hypokalaemia have also been reported.

In case of hepatic dysfunction or rash, consult your doctor.

2.9 What the patient should do in case of a missed dose:

If a dose is missed that dose should be taken as soon as possible. However, if the time of the next dose is near, do not take the dose you have missed but continue your treatment as normal.

Do not take a double dose.

2.10 Information regarding expiry date:

The expiry date is printed on the external and internal packaging.

If the product has passed its expiry date do not use the drug.

2.11 Special precautions for storage:

Protect from sunlight and keep out of reach of children.

Store between 15 - 25°C.

2.12 Date of last revision of the text

Prot. No: 14670/18-4-2002

3. INFORMATION REGARDING THE CORRECT USE OF DRUGS

This medicine has been prescribed for you by your doctor for your specific medical problem only. You should not give it to other people or use it for a different disease, without first consulting your doctor. •If during treatment a problem regarding the drug occurs, immediately notify your doctor or pharmacist. •If there are any questions regarding the information related to the drug you receive or if you need more information about your medical problem, do not hesitate to ask your doctor or pharmacist. •In order for the drug prescribed to you to be effective and safe, it should be taken according to the given instructions. •For your health and safety, it is necessary to read carefully all information related to the drug. •Do not keep drugs in bathroom cupboards because heat and moisture may alter the drug and make it harmful for your health. •Do not keep drugs you no longer require or that have expired. •For greater safety, keep all drugs in a safe place and out of reach and sight of children.

4. LEGAL CATEGORY: Prescription only medicine.

5. PRODUCT LICENCE NUMBER:

•50mg/cap: 23249/02/12.2.2003 **•100mg/cap**: 23250/02/12.2.2003 **•150mg/cap**: 23251/02/12.2.2003 **•100mg/50ml (Vial):** 23252/02/12.2.2003

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