PACKAGE LEAFLET: INFORMATION FOR THE USER

Gynosant®
200 mg hard capsules, Fluconazole

1. IDETIFICATION OF THE MEDICINAL PRODUCT

1.1 Trade name

Gynosant®

1.2 Compostition

Active substance: Fluconazole
Excipients: Lactose monohydrate, Cellulose microcrystalline, Colloidal anhydrous silica, Magnesium stearate, Sodium Lauryl Sulfate, Starch maize pregelatinized.
Composition of empty capsule: Titanium dioxide CI 77891 E171, Gelatin.

1.3 Pharmaceutical form

Capsules hard

1.4 Quantitative composition

Each capsule contains 200 mg fluconazole.

1.5 Nature and contents of the container

Each carton contains 7 or 14 capsules in blister PVC/PVDC – Aluminum and a leaflet.

1.6 Pharmacotherapeutic category

Antimycotics for systemic use - triazole derivatives

1.7 Marketing Authorization Holder

TARGET PHARMA
54 Menandrou st. 104 31, Athens, Greece
Tel.: +30 210.5224830, Fax: +30 210.5224838,
E-mail: info@targetpharma.gr, www.targetpharma.gr

1.8 Manufacturer – Packaging

ΚΛΕΒΑ SA Pharmaceutical Industry,
189 Parnithos Av., Acharnai Attikis
Tel: +30 210 24 02 404-7.

2. WHAT SHOULD THE PATIENT KNOW ABOUT THIS MEDICINE

2.1 General information

Fluconazole is an antifungal agent that is used for the treatment of infection caused by mycetes.

2.2 Indications:

1. Cryptococcal infections, including cryptococcal meningitis and infections of other areas (e.g. lungs, skin). Treatment may receive immuno-competent hosts, patients with AIDS, patients with organ transplantation or other causes of immunosuppression. Fluconazole may also be used for the prevention of relapse of cryptococcal infections in patients with AIDS.

2. Generalised candidiasis, including candidaemia in clinically stable and non-neutropenic patients, scattered candidiasis and focal candidiasis (infections of infections of the peritoneal, endocardial, lung and urinary tract). Also with this drug can be treated, patients with malignant neoplasms or patients who are in intensive care units, as well as patients receiving cytostatic or immunosuppressive treatment. It is obvious that for indications 1 and 2 before the initiation of the treatment the proper tests should be performed such as cultures or other lab tests (microscopy, biopsy, blood tests) so as to identify the causal factor.
3. In-depth endemic fungal infections including coccidiodomycosis, paracoccidioidomycosis, sporotrichosis and histoplasmosis in non-immunosuppressed patients.
4. Mucosal candidiasis: Oropharyngaeal, oesophageal candidiasis, (as alternative of topical treatment), non-invasive bronchopulmonary candidiasis. Candiduria, chronic mucocutaneous candidiasis. Chronic atrophic oral candidiasis (denture sore mouth), as alternative of topical treatment. Patients primarily with disorders of the immune system can be treated with the drug.
5. Genital candidiasis:
   - Vaginal candidiasis as alternative of topical treatment (only as a single administration of one capsule of 150 mg)
     a) acute
     b) re-current as long as the disease has been confirmed by culture.
   - Candidal balanitis.
6. Dermatomycosis, including *tinea pedis, tinea corporis, tinea cruris, tinea versicolor, tinea unguinium* (onychomycosis) and other skin infections caused by Candida.
   Note: Systemic treatment in the above mentioned indications is preferred when the infection is extended in a wide skin area, on the scalp or in patients with impaired defense mechanisms, poor response to topical treatment and persistence of fungal infection despite treatment.
7. Prevention of fungal infections in patients with neutropenia and malignancies, which predispose to the development of such infections as a result of chemotherapy with cytostatic drugs or radiotherapy and after bone marrow transplantation. Attention is drawn to the fact that chronic administration of azoles increases the possibility of developing *C. krusei, Aspergillus, Mucorales, Fusarium, C. glabrata*, strains that are usually resistant to azoles. Treatment may begin before the culture test results are reported, however, as soon as the above mentioned results are available the antifungal treatment should be accordingly adjusted.

Use in children
Fluconazole should not be used for trichophytosis of the scalp.

2.3 Contraindications:

Fluconazole should not be used in patients with known sensitivity to the active substance or to any of its inactive excipients or to similar azole formulations.
Fluconazole should not be co-administered with cisapride or terfenadine known to prolong the QT interval and are metabolized by CYP3A4. (see section 2.5)

2.4 Special warnings and precautions

2.4.1. General

Patients suffering biochemical disorders of liver function during treatment with fluconazole, should be closely monitored for the possibility to develop serious liver damage.
Fluconazole should be discontinued if clinical symptoms and signs appear indicative of liver disease which may be due to the use of fluconazole.
If during treatment any sign of skin rash appears, patients should be closely monitored and the medicine should be discontinued if the rash continue to evolve.
In rare cases, as with the other azoles, anaphylactic reaction has been reported.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. In post-marketing monitoring of the drug, very rare cases of prolongation of the QT interval in electrocardiogram have been reported as well as torsade de pointes in patients who received fluconazole. Although the correlation between fluconazole and prolongation of QT interval has not been adequately substantiated, fluconazole should be administered with caution to patients with possible pro-arrhythmic conditions such as:
- Congenital or acquired QT-prolongation.
- Cariomyopathy, especially when there is heart failure.
- Sinus bradycardia
- Existing symptomatic arrhythmias.

- Concurrent medication which is known to prolong QT interval.
- Electrolyte disorders such as hypokalemia, hypomagnesemia and hypocalcemia. (See section 2.5 Interactions with other medicines or substances)

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

2.4.2. Elderly

If there is no evidence of impaired renal fuction, the usual doses of the procuct should be administered to elderly patients. For cases of renal dysfunction, (creatinine clearance < 50 ml/min) see section 2.6 “Posology in patients with renal disorders”.

2.4.3. Pregnancy

The use of this medicine during should be avoided except for the patients with severe, life-threatening fungal infections for which fluconazole may be used if the expected benefit from the treatment outweigh the potential risk of toxic effects on the fetus.
Women of childbearing potential should use sufficient contraception methods.

2.4.4. Lactation

It is not recommended to nursing mothers.

2.4.5. Children

See section 2.6 Posology

2.4.6. Effect on the ability to drive and use of machines

This product does not affect the ability to drive or use of machines.

2.4.7. Special warnings about the excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

2.5 Interactions with other medicines or substances

As fluconazole may interact with other medicinal products such as anticoagulants, sulfonylureas, hydrochlorothiazide, phenytoin, oral contraceptives, rifampicin, ciclosporine, theophylline, terfenadine, zidovudine, astemizole, benzodiazepines, endogenous steroids, cisapride, rifabutin, tacrolimus, if you take any of these medicines ask your doctor and he will decide what should you do per case.
Concomitant use with cisapride is contraindicated.

2.6 Posology

Adults

1a. For the treatment of cryptococcal meningitis and of cryptococcal infections in other body areas, the usual posology is 400 mg as loading dose in day 1 of treatment and subsequent dose of 200 to 400 mg as a single daily dose. Duration of the treatment depends on the clinical and fungal response to the treatment, usually this duration will be at least 6-8 weeks in cryptococcal meningitis or 10-12 weeks after receipt of negative fungal result in CSF cultivation.

1b. To prevent recurrence of cryptococcal meningitis in AIDS patients, after the treatment of the initial infection, these patients may receive fluconazole indefinitely at a daily dose of 100-200 mg.

2. For the treatment of candidemia, generalized candidiasis and other severe candidiasis, the usual dose of the medicine is 400mg on the first day of treatment, followed by 200mg daily dose. In c ases of inadequate response the dose may be increased to 400mg daily. Treatment duration depends upon patients clinical response.

3. For the treatment of in-depth endemic fungal infections daily dose of 200-400mg should be administered and the treatment may be continued for up to 2 years. The duration of the treatment should be individualized.

4. For the treatment of mucosal candidiasis, the usual dose is 50-100mg once daily for 7-14 days. Treatment should be continued for longer time in patients suffering severe immune system disorders if needed. For the treatment of atrophic oral candidiasis occurring on artificial dentures, the usual dose is 50mg once daily for 14 days, implemented simultaneously with local antiseptic measures on dentures. For the treatment of other mucosal candidiasis infections (other than vaginal candidiasis which is presented below) e.g. pesophagitis, non-invasive bronchopulmonary infections, candiduria, chronic mucocutanous candidiasis etc. the usual effective dose is 50-100mg daily administered for 14-30 days.

5. For the treatment of vaginal candidiasis and candida balanitis, 150mg should be administered orally as a single dose.

6. For skin infections (dermatomycosis) that include *tinea pedis, tinea corporis, tinea cruris, tinea versicolor, tinea unguinium* (onychomycosis) and other skin infections caused by Candida, recommended dose is 150mg as a single weekly dose or 50mg as a single daily dose. The duration of the treatment may vary from 2 to 4 weeks, especially for *tinea pedis* may require treatment for 6 weeks. For pytiriasis versicolor dose should be 50mg daily for 2 to 4 weeks.
   For onychomycosis the recommended dose is 150mg single weekly dose. Treatment should be continued until the infected nail is replaced by new healthy nail. Nail growth in fingers and toes normally takes 3-6 months and 6-12 months respectively. However, growth rate may vary among patients, depending also by the age of the patient. Occasionally, after the successful treatment of long-term infection, nails may remain disfigured.

7. For the prevention of fungal infections in patients at high risk to develop generalized infection, e.g. patients expected to have severe or prolonged neutropenia, such as patients with marrow transplantation, the recommended dose is 400mg daily and for the prevention of fungal infections 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, dose ranges from 50 to 400mg once daily. Administration must start several days before the event of anticipated febrile neutropenia and continue for 7 days after the increase in the number of neutrophil cell values over 1000 cells per mm^3.

Use in children
As with adults with similar infections, the duration of treatment is based on the clinical and fungal response. Fluconazole is administered as a single daily dose.
For children with renal impairment, see dosage in section Patients with renal impairment.

Children older than 4 weeks of age
Recommended dose of fluconazole for mucosal candidiasis is 3 mg/kg daily. Loading dose of 6 mg/kg may be used on the first treatment day to achieve faster stabilization of blood levels. For the treatment of generalized candidiasis and cryptococcal infections, the recommended dose is 6-12 mg/kg daily, depending on the severity of the disease.
For the prevention of fungal infections in immunosuppressed patients at risk of neutropenia as a result of cytotoxic chemotherapy or radiotherapy, the dose should be 3-12 mg/kg daily, depending on the extent and duration of induced neutropenia (see adult dosage).

Maximum dosage of 400mg daily should not be exceeded in children.

Children age 4 weeks or younger
Exertion rate in newborns is very slow. During the first two weeks of life, the same dose in mg/kg should be administered as in older children, but the administration should be every 72 hours. During the 3^{rd} and 4^{th} week of life the same dose should be administered every 48 hours. There are very few pharmacokinetic data to support this dosage in newborns.
Maximum dosage should not exceed 12mg/kg every 72 hours in children during the first two week of life.
For children of 3 to 4 weeks of life the dosage should not exceed 12mg/kg every 48 hours.
Fluconazole pharmacokinetic has not been studied in children with renal failure.

Use in elderly patients
If there is no indication of renal impairment, usual doses of the medicine should be administered. In patients with renal impairment (creatinine clearance < 50 ml/min) dosage should follow the instructions for renal impairment, see next paragraph.

Patients with renal impairment
Fluconazole is eliminated mainly through urine in unchanged form as the administered dose. For single administration of the medicine no dosage adjustment is needed. For multiple dosages of fluconazole in patients with renal impairment, including children, a loading dose of 50 to 400mg should be administered. After loading, daily dose, according to indications, should follow as presented in the scheme of the table below:

Creatinine clearance (ml/min)	**% of recommended dose**
>50	100%
11-50	50%
Patients in hemodialysis	100% after each hemodialysis session

When the value of plasma creatinine is the only marker of renal function, the following formula is used to define creatinine clearance:

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

Women: 0.85 of the respective man value

Administration
Fluconazole may be administered orally or via intravenous infusion at a rate that not exceeding 10ml/min. The route of administration depends on the clinical condition of the patient. When changing the route of administration from intravenous to oral or vice versa, there is no need for a change in the daily dose of the drug. Fluconazole is administered in 0.9% sodium chloride solution. Each 200mg vial (volume of 100 ml) contains 15 mmol Na^+ and Cl^-. Since Fluconazole is available in dilute sodium chloride solution, in patients requiring limitation of sodium or fluid intake, the rate of fluid administration should be considered.

2.7 Overdose – Management

If an overdose occurs, symptomatic treatment is followed (supportive measures and if necessary gastric lavage). As fluconazole is excreted via urine, hemodialysis for 3 hours may reduce plasma drug concentrations by 50%. In case of overdose contact Poison Center Athens Tel.: +30 210 77 93 777.

2.8 Possible side effects:

Fluconazole is generally well tolerated.
The most common adverse drug reactions reported during clinical trials that are related to fluconazole use are:
Nervous system Disorders: Headache
Gastrointestinal disorders: abdominal pain, diarrhea, flatulence, nausea.
Skin and subcutaneous tissue disorders: rash.
Hepatobiliary disorders: Hepatic toxicity including rare cases of deaths, increased blood levels of alkaline phosphatase, bilirubin, SGOT and SGPT. During treatment with fluconazole and comparable drugs, it has been reported disorders in renal function, in the function of the hematopoietic system and also in the function of the liver, for few patients and specifically patients suffering from severe underlying diseases such as AIDS and cancer, (see section 2.4 Special warnings and precautions). The clinical significance and causal relationship to treatment is not confirmed.
Based on the post-marketing experience the following adverse events have been reported:
Blood and the lymphatic system disorders: leukopenia including neutropenia, agranulocytosis and thrombocytopenia.
Immune system disorders: anaphylaxis (including angioedema, face edema, pruritus, urticaria).
Metabolism and nutrition disorders: hypercholesterolaemia, hypertriglyceridaemia, hypokalemia.
Nervous system disorders: dizziness, seizures, taste perversion.
Cardiac disorders: QT prolongation, torsade de pointes (see section 2.4).
Gastrointestinal disorders: dyspepsia, vomiting.
Hepatobiliary disorders: abnormal hepatic function, hepatitis, hepatocellular necrosis, jaundice.
Skin and subcutaneous tissue disorders: alopecia, exfoliative skin disorders, including STEVENS-JOHNSON syndrome and toxic epidermal necrolysis.

Pediatric population:
Profile and incidence of side effects and also any abnormal laboratory findings recorded during clinical trials in children were comparable to those reported for adults.

If you get any side effects, please talk to your doctor or pharmacist or any other health care provider or directly to the National Medicines Agency (284 Mesogion Av., 15562, Cholargos, Athens, Greece www.eof.gr).

2.9 What you should know in case you forget to take one dose:

If you should take this medicine regularly and you forget a dose, you should receive it as soon as you remember. If it is about the time for your next dose, do not take the missed one, continue your treatment plan.

2.10 What should the patient know about the expiration date:

Expiration date is mentioned in outer and immediate container.
Do not use after the expiration date.

2.11 Special warnings about the storage of the product:

The product should be store at temperature below 25ºC.
Keep out of reach and sight of children..

2.12 Date of last revision

13 December 2017

3. INFORMATION FOR THE RATIONAL USE OF MEDICINES

- This pharmaceutical product was prescribed by your doctor to you, according to your medical history and condition. Do not pass the product to others or use it in any other condition even if the symptoms may appear the same and without receiving your doctor's or pharmacist's advice.
- If during treatment with this medicine you experience any problem or issue, contact immediately your doctor or pharmacist.
- If you have any questions regarding the information for this product, its use or about the medical condition that you suffer, you should ask your doctor or pharmacist.
- This product will be safe and effective if it is used exactly according to instructions provided.
- For your own safety it is highly recommended that you read carefully all information provided for the prescribed medicine.
- Do not store medicines in bathroom lockers, as the high temperature and the humidity may degrade the product which may be harmful to your health.
- Store the product in the original packaging.
- If your doctor instructed you to stop the use of this product, dispose the remaining product and do not use it.
- Do not keep the medicine you do not need any more or those that are expired.
- Keep all medicines in safe place out of reach and sight of children.

4. PRESCRIBING INFORMATION

This medicine is subjected to medicinal prescription.