PATIENT INFORMATION LEAFLET

SELFLEKS FLUKOSEL 200 mg/100 mL I.V. Bag Containing Solution for Infusion Administered intravenously
Sterile

- ***Drug substance:*** Each 100 mL PVC Bag contains 200 mg fluconazole.
- ***Excipients:*** Contains sodium chloride and water for injection.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use **high or low** doses other than the recommended dosage.*

What is in this leaflet:

Headings are included.

1. What SELFLEKS FLUKOSEL is and what it is used for?

SELFLEKS FLUKOSEL clear, colorless solution should comply with standards of intravenous use.

It should be in clear, PVC bags.

SELFLEKS FLUKOSEL is one of a group of drugs called antifungal. The active ingredient is Fluconazole. SELFLEKS FLUKOSEL is used to treat infections caused by fungi, including yeasts. It can also be used to prevent you from getting a fungal infection. The most common cause of fungal infections is yeast called *Candida*.

This medicine can be given to you by your doctor to treat the following types of fungal infections.

- Mucosal thrush, mouth or throat infection. Normal or immunocompromised patients can be treated.

- Skin infections - athlete's foot, fungal disease, itching.

- Internal (systemic) fungal infections caused by:
    - Candida in the blood circulation, body organs (heart, lungs), peritoneum, membrane consisting of a row of squamous epithelial tissue covering the inside of the heart, eye or urinary tract
    - *Cryptococcus*, meningitis, and infections in other areas such as lungs and skin
- In patients with adequate immune system, developing systemic fungal diseases

You may also be given SELFLEKS FLUKOSEL for the following.

- Preventing a fungal infection (if your immune system is not working properly). In the prevention of fungal infections in patients who predispose to fungal infections as a result of drug therapy in cell-killing cancer or radiation therapy in cancer due to malignant disease.
- Preventing the return of an infection caused by *Cryptococcus* (in AIDS patients)

Your doctor may begin your treatment before the results of culture and other laboratory studies are known. Once results are available, treatment will be arranged by your doctor as needed.

2. What you need to know before you use SELFLEKS FLUKOSEL
DO NOT USE SELFLEKS FLUKOSEL

If:

- If you are *hypersensitive* to:
    - Any component of SELFLEKS FLUKOSEL
    - Other medicines you take to treat fungal infections.
    - Symptoms of hypersensitivity may include itching, redness of the skin, or difficulty breathing.
- If you are taking terfenadine or astemisol, an antihistamine intended to treat allergies
- If you are taking cisapride used for stomach upset
- If you have schizophrenia and are taking pimozide, an antipsychotic drug
- If you are taking quinidine-containing medication for heart rhythm disorder.

USE SELFLEKS FLUKOSEL CAREFULLY in the following cases

If:

- You have liver or kidney problems
- Your potassium, calcium or magnesium levels in your blood are abnormal
- You have serious illnesses, especially AIDS and cancer
- You are taking medicines that potentially damage or irritate more than one concurrent liver and an underlying disease develops that will kill your liver tissues (hepatic necrosis). If your liver is damaged or irritated with fluconazole, it is reversible. Your doctor will follow you in case of severe liver damage during treatment, if necessary, he may stop your medicine.
- Rash skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome

develop. Your doctor may discontinue your treatment if there is a fluid-filled bubble on the skin, or if there is a hypersensitivity condition that usually goes away spontaneously and causes lace-like rash on the hands, face and feet.

- You use less than 400 mg of terfenadine per day
- Very severe response of the body to allergenic substances, if sudden hypersensitivity develops
- You have any electrolyte disturbances in the blood
- You are using other medicines with fluconazole
- You are taking concomitant medicines that are not destroyed by CYP3A4, an enzyme in the liver, but known to prolong the QT interval on the ECG recording.

Prolongation of the QT interval was observed in the recording of the electrical activity of the heart (ECG) with some azole drugs, including fluconazole.

- You have heart disease, including heart rhythm problems
- There is a congenital or documented condition of the heart that can lead to serious arrhythmias and sudden death
- You have acute, subacute or chronic disease in your heart muscle, especially when there is heart failure
- Your heart beats less than 60 minutes per minute (sinus bradycardia)

Please consult your physician if these warnings apply to you, even at any time in the past.

Use of SELFLEKS FLUKOSEL with food and drink
It is not valid due to the route of administration.

Pregnancy
Consult your doctor or your pharmacist before using the drug.

Do not use SELFLEKS FLUKOSEL during pregnancy unless your doctor tells you otherwise.

If you notice that you are pregnant during your treatment, consult your doctor or pharmacist immediately.

Breast-feeding
Consult your doctor or your pharmacist before using the drug.
Do not use SELFLEKS FLUKOSEL during pregnancy.

Driving and using machines
When driving or operating machinery, it should be noted that occasional dizziness or seizure may occur.

Important information about some of the excipients contained in SELFLEKS FLUKOSEL
SELFLEKS FLUKOSEL contains sodium. This should be considered for patients on a controlled sodium diet.

Use with other medicines

Since they should not be taken with SELFLEKS FLUKOSEL, inform your doctor immediately.

- If you are taking the antihistamine terfenadine or astemizole to treat allergies
- If you are taking cisapride used for stomach upset
- If you are a schizophrenic patient and are taking the antipsychotic medication pimozide
- If you are taking medication containing quinidine for heart rhythm disturbance.

The combined use of SELFLEKS FLUKOSEL and erythromycin, an antibiotic, is not recommended.

Tell your doctor if you are taking any of the following medicines. Some drugs that may interact with SELFLEKS FLUKOSEL are as follows, their use with these medicinal products requires precaution and dose adjustment:

- Alfentanil, fentanyl used in anesthesia
- Amitriptyline and nortriptyline used to treat depression
- Amphotericin B used for severe fungal diseases
- Warfarin (or similar drugs) that thin the blood to prevent blood clots
- Azithromycin, an antibiotic
- Benzodiazepines, such as midazolam, triazolam, that help you sleep or to counter anxiety
- Calcium channel blockers such as nifedipine, isradipine, amlodipine and felodipine, which are used in blood pressure lowering and some heart diseases.
- Celecoxib used in the treatment of joint arthritis
- Cyclophosphamide used in cancer treatment
- Halofantrine used to treat malaria
- HMG-Co A reductase inhibitors used for lipid disorders that are metabolized by CYP3A4, such as atorvastatin and simvastatin, or by CYP2C9, such as fluvastatin.
- Losartan, a blood pressure lowering drug
- Methadone used in the treatment of heroin addiction
- Pain, fever and inflammation effective drugs such as naproxen, lornoxicam, meloxicam, diclofenac
- Oral contraceptives, birth control drugs
- Endogenous steroids
- Prednisone used for acute organ rejection and antiinflammation
- Saquinavir used in the treatment of AIDS disease
- Vinca alkaloids used in the treatment of various cancers

- Vitamin A
- Diabetes medications such as chlorpropamide, glibenclamide, glipizide or tolbutamide
- Diuretic tablets such as hydrochlorothiazide used to treat fluid retention and high blood pressure
- Phenytoin, carbamazepine used to control epilepsy
- Rifampicin or rifabutin, which are antibiotics for infections
- Cyclosporine or tacrolimus to prevent transplant rejection
- Theophylline used to control asthma
- Zidovudine, also known as AZT, used in patients with AIDS
- Halofantrine

If you are currently using or taking any prescription or over-the-counter medication, please inform your doctor or pharmacist.

3. How to use SELFLEKS FLUKOSEL

Instructions for appropriate use and dose / administration frequency:

The daily dose of fluconazole should depend on the type and severity of the fungal infection. For types of infections that require treatment with repeated doses, treatment should be continued until clinical parameters or laboratory tests indicate that the active fungal infection has passed. An insufficient duration of treatment causes a recurrence of active infection. To prevent relapse; Maintenance treatment is often required in patients with AIDS and a type of fungal disease of the mouth and pharynx called cryptococcal meningitis or recurrent oropharyngeal candidiasis.

Unless recommended otherwise by the doctor, the following doses can be applied:

Mucosal moniliasis – dose depends on the area that is infected	50 mg per day for a period of 7-14 or 14-30 days. The dosage can sometimes be increased to 100 mg. If you're an AIDS patient, a single dose of 150 mg/week can be administered after complete primary cure, in order to prevent recurrence. For atrophic fungal disease connected with the usage of prosthesis the routine fluconazole dose is, 50 mg per day for 14 days, together with local antiseptic measures applied on the prosthesis.
Fungal skin infections	50 mg per day for a period of 2-4 weeks (For athletic foot it can be increased to 6 weeks)
Systemic fungal infections	400 mg on the first day and after that 200-400 mg per day for a period of 6-8 weeks or longer if necessary. If you're an AIDS patient, you can use 200 mg/day for indefinitely after complete primary cure, in order to prevent recurrence.
To prevent catching a fungal infection	50-400 mg per day when you have a risk of catching an infection. If you have a high risk of systemic infection the dose is 400 mg / day. Fluconazole

	administration should begin a few days before the onset for patients with a predicted decreased number of fragmented cell count (neutropenia) and should be continued for 7 more days after the neutrophil count increases above 1000/ mm^3.
Prevent recurrence of an infection due to Cryptococcus (a type of fungal infection)	100-200 mg/day indefinitely
For systemic fungal diseases occurring in patients with adequate immune systems	Between 11-24 months for Coccidioidomycosis Between 2-17 months for Paracoccidioidomycosis, Between 1- 16 months for sporotrichosis and Between 3-17 months for histoplasmosis, The appropriate duration should be selected for each patient

Route and method of administration:
It is administrated intravenously.

This drug will be administered to you by your doctor or your nurse through slow injection (infusion) into your vein over 30 minutes.

SELFLEKS FLUKOSEL is provided as a solution. It shouldn't be diluted more. This drug should not be mixed with another drug before infusion.

Various age groups:

Use in children:

4 weeks- 15 years	Mucosal infections	3 mg/kg once a day. 6 mg/ kg on the first day.
	Systemic fungal Infections	6-12 mg/kg once a day.
	Prevention of fungal infections	When there's a risk of catching an infection 3-12 mg/kg once a day
3-4 weeks	The same dosage as mentioned above, but administered once per two days.	
Less than 2 weeks	The same dosage as mentioned above, but administered once per three days. Maximum dose for once per three days 12 mg/kg.	

The maximum dose of 400 mg / day should not be exceeded in children.

Use in the elderly:

Normal adult dose will be administrated if you don't suffer from any renal problems.

Special conditions of use:

Renal failure:

No dose adjustment is required in a treatment that requires a single dose. In multiple dose treatments, your doctor will regulate the dose to be given, including children.

Hepatic failure:

No data available.

Please talk to your physician or pharmacist if you feel that the effect of SELFLEKS FLUKOSEL is too strong or too weak.

If you have used more SELFLEKS FLUKOSEL than you should

If you have used more SELFLEKS FLUKOSEL than you should, talk a physician or pharmacist.

If you forget to use SELFLEKS FLUKOSEL

Since this drug is administered to you under close medical monitoring it is not very probable to skip a dose. Even then, if you think a dose is skipped inform your doctor or pharmacist.

Effects which may occur when treatment with SELFLEKS FLUKOSEL is discontinued

Do not stop taking SELFLEKS FLUKOSEL unless your doctor tells you. In cases where you need to stop taking SELFLEKS FLUKOSEL, your doctor will determine the best method for you. If you have any questions about the use of SELFLEKS FLUKOSEL, consult your doctor.

4. What are the possible side effects?

As with all medicines, there may be side effects in people who are sensitive to the ingredients of SELFLEKS FLUKOSEL.
The frequency of adverse events is reported using the following categories.

Very common	: can be seen at least 1 of 10 patients.
Common	: can be seen less than one in 10 patients, but more than one in 100 patients.
Uncommon	: can be seen less than one in 100 patients, but more than one in 1,000 patients.
Rare	: can be seen less than one in 1.000 patients, but can be seen more than 10,000 patients in one.
Very rare	: can be seen less than one in 10,000 patients.
Unknown	: cannot be estimated from available data.

Common:

- Headache
- Abdominal pain
- Nausea
- Vomiting
- Discomfort in the stomach
- Diarrhea
- Gas

- Rash
- High alkaline phosphatase (ALP) levels
- Increase in aspartate aminotransferase (AST)
- Increase in blood alkaline phosphatase

Uncommon:

- Insomnia
- Sleepiness
- Seizures
- Drowsiness
- Numbness
- Distorted sense of taste
- Dizziness due to balance disorder (vertigo)
- Indigestion, dyspepsia
- Gas and dryness of the mouth
- Slowing down or stopping of bile juice
- Hepatitis
- Increased bilirubin
- Itching
- Urticaria
- Increased sweating
- Muscle pains
- Tiredness
- Unwellness
- Weakness
- Fever

Rare:

- Rare serious allergic reactions, including:
- Sudden wheezing, difficulty breathing or tightness in the chest,
- Swelling of the eyelids, face or lips,
- Itching, reddening or itchy red spots on the whole body,
- Skin rash,
- Severe skin reactions such as rash (which may also affect the mouth and tongue) causing swelling (severe skin reactions are more likely in patients with AIDS)
- If you are experiencing any of the symptoms such as a serious disease (toxic epidermal

necrolysis) with liquid-filled blisters on the skin, immediately inform your doctor.

- Decrease in the number of white blood cells
- Decrease in the number of platelets-blood platelets
- High cholesterol
- High triglycerides
- If the blood potassium level is above normal
- Trembling
- QT prolongation
- Life-threatening irregular heart rhythm (Torsades de pointes)
- Liver-related toxicity, also rarely leading to death
- Liver failure
- Liver inflammation
- Jaundice
- Damage and death of liver tissues
- Inflammation with blood, swelling and redness on the skin and around the eyes (Stevens-Johnson syndrome)
- Acute widespread rash skin diseases including inflamed blisters marked by redness or blistering on the skin.
- Edema o face
- Hair loss

Pediatric patients

The adverse event incidence and models recorded during pediatric clinical studies and the laboratory abnormalities are comparable to those observed in adults.

If you experience any side effect not mentioned in this patient information leaflet, inform your doctor or your pharmacist.

Reporting of the side effects:

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store SELFLEKS FLUKOSEL

Keep SELFLEKS FLUKOSEL out of the sight and reach of children, and in its packaging.

Store at room temperature below 25°C, within its original packaging. Do not use if the solution is not clear, contains particles, or the bag is damaged. The rest of the solution, some of which has been spent, is not used again.

It should be used immediately after opening.
Use in compliance with the expiry date.
Do not use SELFLEKS FLUKOSEL after the expiration date stated on the packaging.

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This patient information leaflet was approved on .../.../...

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THE FOLLOWING INFORMATION IS FOR MEDICAL PERSONNEL WHO WILL ADMINISTER THIS MEDICINE

Fluconazole is administered both orally and in the form of an intravenous infusion at a rate not exceeding 10 ml per minute. The method of administration depends on the clinical condition of the patient. There is no need to change the daily dose when switching from intravenous to oral or otherwise.

SELFLEKS FLUKOSEL injectable form is formulated in 0.9% sodium chloride solution and each 200 mg (100 mL PVC bag) contains 15 mmol Na^+ and the same amount of Cl^-. Since SELFLEKS FLUKOSEL contains a dilute salt solution, attention should be paid to the rate of fluid administration in patients requiring sodium or water restriction. SELFLEKS FLUKOSEL intravenous infusion is compatible with the following administration fluids.

a) 20% Dextrose
b) Ringer's solution
c) Hartmann solution
d) Potassium chloride in dextrose
e) 4.2% Sodium bicarbonate
f) Aminofusin
g) Physiological saline

SELFLEKS FLUKOSEL may be infused in one of the above fluids from an existing IV set. Although no specific incompatibility has been observed, mixing it with any other drug before infusion is not recommended.

Parenteral preparation products before use, the solution and packaging should be checked to see if they contain as many particulates as permitted and if the color is impaired (see precautions).

Do not use products that are not clear and unpacked.

To open: tear the outer packaging from the top and remove the solution container. Some opacity can be seen on the plastic due to the absorption of moisture during the sterilization process. This is normal and does not affect the quality and reliability of the solution. Opacity will disappear over time.

Preparation for administration: (use aseptic technique)

1- Turn off the current control lock (clamp) of the administration set.
2- Remove the lid from the exit hole under the medicine bag.
3- Insert the needle of the administration set into the hole until the set is firmly seated.
4- Hang the bag on the suspension.
5- Tighten and release the chamber where the drop flows to ensure smooth fluid flow in the chamber.
6- Open the Flow Control Lock and remove the air from the set. Close the lock.
7- Connect the set to the venipuncture device. If the serum is not flowing, adjust the venipuncture.
8- Adjust administration speed with Flow Control Lock.

ATTENTION:
DO NOT USE FLEXIBLE BAGS IN MULTIPLE CONNECTIONS.
FOR SINGLE-DOSE USE.
I.V. USE
DO NOT ADD ADDITIVES TO THIS SOLUTION.
USE ONLY CLEAR SOLUTION AND UNOPENED PACKAGE.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SELFLEKS FLUKOSEL 200 mg/100 mL I.V. Bag Containing Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL bag:

Drug substance:	
Fluconazole	200 mg
Excipients:	
Sodium Chloride	900 mg
Water for Injection	q.s. 100 mL

Please see section 6.1 for excipients.

3. PHARMACEUTICAL FORM

SELFLEKS FLUKOSEL is a solution for infusion.
The clear and colorless solution must comply with the parenteral standards.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment can be started before the results of culture and other laboratory results are reported. However, once these results are available, the treatment must be arranged accordingly.

SELFLEKS FLUKOSEL is indicated for the treatment of the following conditions:

1. Cryptococcosis including the cryptococcal meningitis and infections of other organs (lungs, skin, etc.). AIDS patients, individuals after organ transplantation or with other causes of immunosuppression or with normal immunity can be treated with this drug. Fluconazole can be used as the maintenance therapy in patients with AIDS to prevent the recurrence of cryptococcal disease.

2. Systemic candidiasis including candidemia, disseminated cancidiasis and other forms of invasive candidiasis. These include the infections of peritoneum, endocardium, eyes, lungs and urinary tract infections. Patients with malignant diseases, hospitalized in intensive care units, receiving cytotoxic or immunosuppressive treatments or having other factors that create predisposition to candida infections can be treated with this drug.

3. Mucosal candidiasis. These include the oropharyngeal, esophageal, non-invasive bronchopulmonary infections, candiduria and mucocutaneous candidiasis (mouth sores related to prostheses). Patients with normal or impaired immune functions can be treated. It can be used to prevent the recurrence of the oropharyngeal candidiasis in patients with AIDS.

4. In can be used to prevent fungal infections in patients with predisposition for fungal infections after chemotherapy or radiotherapy administered because of malignant diseases.

5. In deep endemic mycosis infections including coccidioidomycosis, paracoccidioidomycosis, sporotrichosis or histoplasmosis in patients with adequate immune system.

4.2. Posology and method of administration

Posology /administrationfrequency and duration

The daily dosage of fluconazole must be related with the type and severity of the infection. For the infection types requiring treatment with repeated dosages, the treatment must continue until the parameters or laboratory tests show that the active fungal infection has been cured. Insufficient treatment period will cause recurrence of the active infection. Maintenance therapy will be required frequently to prevent recurrence in patients with AIDS or patients with cryptococcal meningitis or recurring oropharyngeal candidiasis.

The following dosages can be administered unless otherwise is recommended by the doctor:

Adults

1. The routine dosage in cryptococcal meningitis or cryptococcal infections in other areas is 400 mg in day 1, and 200-400 mg once daily in following days. Although the treatment period in Cryptococcus infections depends on the clinical and mycological response, it is at least 6 to 8 weeks for cryptococcal meningitis.

Fluconazole can be used in a dosage of 200 mg daily for an indefinite period of time in patients with AIDS to prevent the recurrence of cryptococcal meningitis.

2. The routine day 1 dosage in candidemia, disseminated candidiasis and other invasive candidal infections is 400 mg and 200 mg for the following days. The latter can be increased up to 400 mg daily based on the clinical response. The period of treatment will depend on clinical response.

3. The routine dosage for oropharyngeal candidiasis is 50 -100 mg once a day for a period of 7 to 14 days. The treatment can be extended for a longer period if required in patients with seriously impaired immune functions. The routine fluconazole dosage for atrophic oral candidiasis related to prosthesis use 50 mg once a day for a period of 14 days.
The routine effective dosage for the other candidal infections of the mucosa (excluding vaginal candidiasis, see below), for example esophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutaneous candidiasis etc., is 50-100 mg given for 14 to 30 days.

After administering the primary treatment in patients with AIDS, a single dosage of 150 mg once weekly can be given to prevent the recurrence of oropharyngeal candidiasis.

4. The fluconazole dosage recommended to prevent candidiasis is 50-400 mg once daily depending on the risk of fungal infection development. The dosage recommended for patients with high risk of systemic infection including those with deep or long-lasting neutropenia is 400 mg once daily. Fluconazole administration must be started a few days before the start of expected neutopenia, and must be continued for 7 days more after the neutrophil count exceeds 1000/ mm^3.

5. The daily dosages of 200-400mg can be required for deep endemic mycoses for periods up to 2 years. While the routine treatment period is 11 to 24 months for coccidioidomycosis, 2 to 17 months for paracoccidioidomycosis, 1 to 16 months for sporotricosis and 3 to 17 months for histoplasmosis, the treatment period must be selected specifically for each patient.

Method of administration:

SELFLEKS FLUKOSEL infusion solution is administered intravenously.

Fluconazole is administered both orally and as intravenous infusion with a rate not exceeding 10 mL/ minute. The way of administration depends on the clinical conditions of the patient. There will be no need to change daily dosage when shifting from intravenous route to oral route or vice versa. Injectable form of SELFLEKS FLUKOSEL is formulated within sodium chloride solution 0.9% and since each 200 mg (in 100 mL PVC bags) contains 15 mmol Na^+ and Cl^- in the same amount. SELFLEKS FLUKOSEL intravenous infusion is compatible with the following administration fluids.

a) 20% Dextrose
b) Ringer solution
c) Hartmann solution
d) Potassium chloride in dextrose
e) 4.2% Sodium bicarbonate
f) Aminofusin
g) Physiologic Saline Water

SELFLEKS FLUKOSEL can be given in one of the solutions given above through any IV infusion set. Although no specific incompatibility has been observed, it is not recommended to mix the infusion fluids with any other drug.

Additional information for special populations:

Renal Failure:

Fluconazole is largely excreted in unchanged drug form, and does not require dosage adjustment for treatments with one single dosage. An initial loading dose of 50 mg to 400 mg must be administered in patients with impaired renal functions including children who will receive multiple fluconazole dosages. Following the loading dose, the daily dosage (based on the indication) must be arranged according to the following table:

Creatinine clearance (mL/min)	Recommended dose percentage
> 50	100%
≤50 (not under dialysis)	50%
Patients receiving dialysis regularly	100% after each dialysis seance

Pediatric population:
Like in the similar infections of adults, treatment depends on clinical and mycological response. The maximum adult daily dose must not be exceeded in children. Fluconazole is administered as one single daily dose.

Use in children older than four weeks of age:

The dose recommended for the treatment of mucosal candidiasis is 3 mg/kg/day. A loading dose of 6 mg/kg can be used to reach the steady state levels more quickly.

The dose recommended for the treatment of systemic candidiasis and cryptococcal infections is 6-12 mg/kg/day depending on the severity of the disease.

The recommended daily fluconazole dose in pediatric patients with AIDS to prevent recurrence of cryptococcal meningitis is 6 mg/kg.

In patients with immune system insufficiency considered as risky because of neutropenia that have occurred following cytotoxic chemotherapy or radiotherapy, dose must be 3-12 mg/kg/day to prevent fungal infections depending on the period and level of neutropenia (see: adult dosages). (For use in children with impaired renal functions, see Renal Failure).

The maximum daily dose in children must not exceed 400 mg.

Use in infants four months of age or younger:

Excretion of fluconazole in newborns is slow. The 12 mg/kg dosage recommended for older children is suitable for the first two weeks of life; however, this dosage must be administered every 72 hours. The same dose must be administered every 48 hours to infants 3 or 4 weeks of age.

The maximum dosage of 12 mg/kg administered every 72 hours must not be exceeded in infants two weeks of age. In children 3 to 4 weeks old, a dose of 12 mg/kg must not be exceeded every 48 hours.

Geriatric population:
The recommendations for normal dosage must be adopted in cases that there are no evidences of renal impairment. Dosage must be adjusted as described in the renal failure section in patients with renal impairment (creatinine clearance < 50 mL/min).

4.3. Contraindications

SELFLEKS FLUKOSEL must not be used in patients known to be sensitive against this drug or any of its inert components or similar azole compounds.

According to studies on the interactions of multiple dosages, use of terfenadine together with fluconazole is contra-indicated in patients who take fluconazole in dosages equal to greater than 400 mg. Concurrent administration of drugs including cisapride, astemizole, pimozide and quinidine, which are known to extend the QT interval and metabolized with

P450(CYP) 3A4 enzyme is contraindicated in patients taking fluconazole (See: Section 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction).

4.4. Special warnings and special precautions for use

Fluconazole must be administered with care to patients with liver dysfunctions.

Some abnormalities in the hematologic, hepatic, renal and other biochemical test results have been observed during the treatment with SELFLEKS FLUKOSEL in patients particularly with serious underlying diseases including AIDS or cancer; however, the clinical significance of these and their relation with treatment are unclear.

Postmortem findings including hepatic necrosis have been found very rarely in patients who have died because of underlying diseases and had received multiple doses of SELFLEKS FLUKOSEL. These patients had received concurrently more than one drug, some of them known to be hepatotoxic and/or had underlying conditions that might lead to hepatic necrosis. Serious hepatic toxicity cases including death have been observed in patients with severe medical conditions and treated with fluconazole. As regards hepatotoxicity related to fluconazole, no clear relations were observed between the age of gender of the patient and the period of treatment and total daily dose. Fluconazole hepatotoxicity has generally been reversible following stopping of the treatment. Patients with abnormal liver tests anytime during fluconazole treatment must be followed against any risk of more serious hepatic damage development. Fluconazole must be stopped in case clinical findings or symptoms develop that might be consistent liver disease related to fluconazole.

Exanthematous skin reactions including toxic epidermal necrosis and Stevens- Johnson syndrome have been developed during treatment with fluconazole. The tendency of having intense skin reactions against many drugs is higher in AIDS patients. In case any skin eruption that might be attributed to fluconazole is observed in patient treated for superficial fungal infection, treatment with this agent must be stopped. In case skin eruptions develop in patients with invasive/systemic fungal infections, these must be followed-up closely, and fluconazole must be stopped if bullous lesions or erythema multiforme develop.

Patients taking terfenadine together with fluconazole less than 400 mg daily must be followed-up carefully (See: Section 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction).

Anaphylaxis has reported in rare cases, like with other azole compounds.

Some azole compounds including fluconazole have been related to QT-interval elongation in electrocardiograms. During the post-marketing observations, QT-interval elongation and torsade de pointes cases were seen very rarely in patients taking fluconazole. The cases were those with risk factors that might contribute to the condition including drug use together with structural cardiac diseases or electrolyte imbalances.

Although the relation between fluconazole and QT prolongation has not been determined fully, fluconazole must be used carefully in patients with potential pro-arrhythmic conditions:
• Congenital or acquired documented QT prolongation
• Cardiomyopathy – particularly together with cardiac insufficiency
• Sinus bradichardia
• Existing symptomatic arrhythmias
• Concurrent use of drugs not metabolized with CYP34A, but known to prolongation the QT interval
• Electrolyte imbalances including hypokalemia or hypomagnesemia

Fluconazole must be used with care in patients with renal dysfunction (See: Section 4.2 Posology and method of administration).

Fluconazole is a potent inhibitor of CYP2C9, and medium inhibitor of CYP3A4. Patients treated concurrently with fluconazole and drugs with narrow therapeutical windows and metabolized with CYP2C9 and CYP3A4 enzymes must be followed-up (See: Section 4.5 Interactions with other medicinal products and other forms of interaction).

This medical product contains 900 mg sodium in each dose. This must be taken this into consideration for patients having a diet with controlled sodium.

4.5. Interaction with other medicinal products and other forms of interaction

Contraindications for use with the following other medical products:

Cisapride:

Some cardiac events including Torsades de pointes have been reported in patients that fluconazole was administered concurrently with cisapride. It has been shown in a controlled study that concurrent administration of fluconazole 200 mg once daily and cisapride 20 mg four times daily will cause increase in cisapride plasma levels and elongation of the QT interval. It is seen that in most of these cases, patients had tendency for arrhythmias or had serious underlying disease; furthermore, the relation between the reported events and the possible drug interaction between fluconazole and cisapride are unclear. Based on the potential severity of such interactions, treatment of patients already taking fluconazole with cisapride is contraindicated (See: Section 4.3 Contraindications).

Terfenadine:

Interaction studies have been carried out upon observation of serious cardiac arrhythmias secondary to elongation of the QTc interval in patients taking azole group antifugal drugs together with terfenadine. A study performed with 200 mg fluconazole daily was not successful in showing the elongation of QTc interval. In another study carried out with fluconazole 400 mg and 800 mg daily, fluconazole raised the plasma levels or terfenadine significantly. Use of fluconazole in dosages ≥ 400 mg together with terfenadine is contra-indicated (See: Section 4.3 Contraindications). Patients taking fluconazole less than 400 mg daily together with terfenadine must be followed-up carefully. For the patients taking fluconazole and terfenadine concurrently, palpitation, tachycardia, vertigo and chest pain cases have been reported spontaneously; the relations between the reported adverse events in these cases and the treatment or the underlying medical disorders are unclear. Based on

the potential severity of such an interaction, not combining the intakes of terfenadine and floconazole is not recommended (See Section 4.3 Contraindications).

Astemizole:

This increase in plasma concentrations of astemizole can lead to QT prolongation and the formation of "Torsades de pointes (TDP)" type ventricular arrhythmias, which are rarely life-threatening. Concurrent use of fluconazole and astemizole is contraindicated (See Section 4.3 Contraindications).

Pimozide:

Although *in vitro* or *in vivo* studies have not been performed, use of fluconazole together with pimozide can cause inhibition of the pimozide metabolism. The increase in pimozide plasma concentrations can cause prolongation of QT and occurrence of TdP rarely. Administration of fluconazole concurrently with pimozide is contra-indicated (See Section 4.3 Contraindications).

Use together with the medical products is not recommended:

Erythromycin:
The concurrent use of fluconazole and erythromycin has the potential of causing cardiotoxicity (prolongated QT interval, TdP) and consequently, sudden cardiac death.
This combination must be avoided.

Adjustment of dosage will be required when using concurrently with the following medicinal products:

Effects of other medicinal products on fluconazole

Hydrochlorothiazide:
In a kinetic interaction study, administration of hydrochlorothiazide in multiple dosages to healthy volunteers taking also fluconazole increased the plasma levels of fluconazole by 40%. Although an effect in these levels will not require the dosage regime in patients using diuretics together with fluconazole, it must be kept in mind by the practitioner.

Rifampicin:
Rifampicin used concurrently with fluconazole had caused reducing of the area under the curve (AUC) of fluconazole by 25% and half-life by 20%. Increasing the dosage of fluconazole must be considered in patients receiving rifampicin concurrently.

Effects of fluconazole on other medicinal products

Fluconazole is a potent inhibitor of CYP2C9 isoenzyme and a moderate CYP3A4 inhibitor. In addition to the observed/documented interactions explained below, the risk of plasma concentration increase risk exists for the drugs administered concurrently with fluconazole and metabolized by CYP2C9 and CYP3A4. Therefore, care must be given when using these combinations and patients must be monitored carefully. The effect of inhibition by fluconazole on the enzyme lasts for 4 to 5 days after stopping fluconazole treatment because of the long half life of fluconazole (See Section 4.3 Contraindications).

Alfentanile:
In a study, $T_{1/2}$ of alfentanile and decreases in clearance and distribution volume were observed following concurrent treatment with fluconazole. The possible mechanism of action is the inhibition of CYP3A4 by fluconazole. Adjustment of alfentanil dosage should be necessary.

Amitriptyline, nortriptyline:
Fluconazole increases the effects of amitriptyline and nortriptyline. 5-nortriptilin and/or S-amitriptyline can be measured at the beginning of combination therapy and one week later. Amitriptyline/nortriptyline dosage must be adjusted if necessary.

Amphotericine B:
Concurrent administration of fluconazole and amphotericine B to infected normal and immunosuppressed mice have given the following results: Small, additional antifungal effect in case of systemic infection with *C. albicans*, no effect on intracranial infection with *Cryptococcus neoformans* and antagonism of the two drugs in systemic infection with *A. fumigatus*. The clinical significance of these results obtained from these clinical studies is unknown.

Anticoagulants:
In an interaction study, fluconazole increased the prothrombin time (12%) in healthy males after warfarin use. In the post-marketing experience bleeding events (bruises, epistaxis, gastrointestinal bleeding, hematuria and melena) in relation with the elongation of prothrombin time have been reported like in other azole antifungal drugs. Prothrombin time must be followed carefully in patients taking coumarin-type anticoagulants. Adjustment of warfarin dosage might be necessary.

Azithromycin:
In an open, randomized, three-way crosswise study carried out on 18 healthy individuals, the mutual effects of the two drugs on the pharmacokinetics of each other were evaluated with the use of 1200 mg oral single dose azithromycin and 800 mg oral single dose fluconazole. No significant pharmacokinetic interaction was found between fluconazole and azithromycin.

Benzodiazepines (short acting):
Following the oral administration of midazolam, fluconazole had caused marked increases in the concentration and psychomotor effects of midazolam. This effect on midazolam appears more prominently following the oral administration of fluconazole as compared to the fluconazole administered intravenously. In case of a requirement of concurrent administration or benzodiazepines in patients treated with fluconazole, reducing the dosage of benzodiazepine must be considered and the patients must be monitored as required.

Fluconazole increases the area under the curve (AUC) of triazolam (single dose) by about 50%, Cmax level by 20-32% and t½ level by 25-50% in relation with the inhibition of triazolam metabolism. Adjustment of triazolam dosage might be necessary.

Carbamazepine:
Fluconazole inhibits the carbamazepine metabolism; an increase of 30% has been observed in serum carbamazepine. The risk of carbamazepine toxicity is present. Adjustment of carbamazepine dosage might be necessary depending on the concentration measurements /effects.

Calcium canal blockers:
Certain dihydropyridine calcium canal antagonists (nifepidine, isradipine, amlodipine and felodipine) are metabolized by CYP3A4. Fluconazole has the potential of increasing the systemic exposure to calcium canal antagonists. Frequent monitoring is recommended for adverse effects.

Celecoxib:
During concurrent administration of fluconazole (200 mg daily) and celecoxib (200 mg), the C_{maks} and UAC levels of celecoxib increased by 68% and 134%, respectively. Administration of half the celecoxib dosage might be necessary when combined with fluconazole.

Cyclosporine:
In a kinetic study carried out on patients with kidney transplantations, it was found that 200 mg/day fluconazole gradually increased the cyclosporine levels. Together with this, in another repeated dosage study, fluconazole 100 mg/day did not affect the cyclosporine levels in patients with bone marrow transplantations. Monitoring of cyclosporine plasma levels is recommended in patients using fluconazole. Fluconazole increases the cyclosporine concentration and UAC level significantly. This combination can be used by reducing the cyclosporine dosage based on the cyclosporine concentrations.

Cyclophosohamide:
Treatment with cyclophosphamide and fluconazole combination causes increases in serum bilirubin and serum creatinine levels. This combination can be used by paying more attention to the risk of increase in bilirubin and serum creatinine.

Fentanyl:
One morality was reported related to possible interaction between fentanyl and fluconazole. The investigator had decided that the patient died because of fentanyl intoxication. In addition to this, in a randomized crosswise study on 12 healthy volunteers, it was shown that fluconazole significantly delayed the elimination of fentanyl. The increase in fentanyl concentration can cause respiratory depression.

Halofantrine:
Fluconazole can increase the plasma concentrations of halofantrine through the inhibition of CYP3A4.

HMG-CoA reductase inhibitors:
The risk of myopathy or rhabdomyolysis will increase if fluconazole is administered together with HMG-Co A reductase inhibitors metabolized by CYP3A4 including atorvastatin and simvastatin or those metabolized by CYP2C9 including fluvastatin. In case concurrent treatment is required, the patient must be monitored as regards the symptoms of myopathy and rhamdomyolysis symptoms, and creatinine kinase must be monitored. HMG-Co A reductase inhibitors must be stopped in case marked increase is observed in creatinine kinase, or diagnosis of myopathy/rhabdomyolysis is made or suspected.

Losartan:
Fluconazole inhibits the losartan metabolism to its active metabolite (E-31 74), which is responsible for the major part of angiotensin II-receptor antagonism during treatment with losartan. Patients must monitor their blood pressure continuously.

Metadone:
Fluconazole can increase the serum concentration of metadone. Adjustment of methadone dosage might be necessary.

Non-steroidal anti-inflammatory drugs:
The C_{maks} and UAC values of flurbiprofen have increased by 23% and 81% when administered together with fluconazole as compared to use administration by itself. Likewise, when racemic ibuprofen (400 mg) was administered together with fluconazole, the C_{maks} and UAC values of the pharmacologically active isomer [S-(+)- ibuprofen] have increased by 15% and 82%, respectively.

Although it had not been investigated specifically, fluconazole has the potential of increasing the systemic exposure to other NSAIDs (e.g. naproxen, lornoxicam, meloxicam, diclofenac), which are metabolized by CYP2C9. It is recommended that NSAIDs should be monitored with short intervals as regards adverse events and toxicity. Adjustment of NSAID dosage might be necessary.

Oral contraceptives:
Two kinetic studies have been carried out by using fluconazole in multiple doses together with combined oral contraceptives. While the area under the curve of ethynil estradiol and norethindrone increased by 40% and 24%, respectively with fluconazole 200 mg daily, in the fluconazole study with 50 mg/day, to marked changes were observed in the levels of both hormones. In a study that fluconazole 300 mg was administered weekly, the area under the curve (UAC) of ethynil estradiol and norethindrone were increased by 24% and 13%, respectively.

Therefore, no effects are expected from multiple dosages of fluconazole on the efficacy of combined oral contraceptives with these dosages.

Endogenous steroids:
50 mg/day Fluconazole does not affect endogenous steroid levels. The daily dosage of 200-400 mg in healthy male volunteers does not have clinically significant effects on endogenous steroid levels or response stimulated by ACTH.

Phenytoin:
Fluconazole inhibits the hepatic metabolism of phenytoin. Use of fluconazole and phenytoin together will significantly increase the clinical phenytoin levels. In case the concurrent use of these two drugs is necessary, the serum phenytoin level must be monitored to prevent phenytoin toxicity, and phenytoin dosage must be adjusted to maintain the therapeutical levels.

Prednisone:
There is a report stating that acute adrenal cortex insufficiency had developed in a patient with liver transplantation and treated with prednisone when the three-month treatment with fluconazole was stopped. Stopping fluconazole had probably caused increase in CYP3A4 activity and this in turn had caused increase of prednisone metabolism. Patients receiving long-term treatments with fluconazole and prednisone must be monitored carefully as regards adrenal cortex insufficiency when fluconazole is stopped.

Rifabutin:
It has been reported that fluconazole interacts with rifabutin and causes increases in serum concentrations of rifabutin reaching 80% when it is used together with rifabutin. Uveitis

has been reported in patients that fluconazole and rifabutin are used concurrently. Patients using fluconazole and rifabutin concurrently must be monitored carefully.

Sakinavir:
Fluconazole increases the UAC value of sakinavir by about 50% and C_{max} level by about 55%, and decreases the sakinavir clearance by about 50% through inhibition of metabolism by düzeyini CYP3A4 and inhibition through P-glycoprotein. Adjustment of sakinavir dosage might be necessary.

Sirolimus:
Fluconazole increase the plasma concentrations of sirolimus probably through inhibition of sirolimus metabolism through CYP3A4 and P-glycoprotein. This combination can be used by adjusting the dosage of sirolimuys based on the effect/concentration measurements.

Sulfonylurea drugs:
It has been shown on healthy volunteers that, when fluconazole is administered to healthy volunteers together with sulfonylurea compounds (chlorpropamide, glibenclamide, glipizide, tolbutamide), the half life in serum are prolongated. Fluconazole may be used in combination with oral sulfonylureas in diabetic patients, but the possibility of a hypoglycemic episode should always be kept in mind. Monitoring the blood glucose levels frequently and adjusting the sulfonylurea dosages accordingly are recommended.

Tacrolimus:
Fluconazole can increase the serum concentrations of tacrolimus administered orally up to 5 folds through the inhibition of CYP3A4 in intestines. No significant pharmacokinetic changes were observed when tacrolimus was administered through the intravenous route. The increase in tacrolimus was related to nephrotoxicity. The oral tacrolimus dosage must be decreased in proportion with tacrolimus concentration. An interaction has been reported causing increase in tacrolimus serum concentrations when fluconazole and tacrolimus are administered concurrently. Nephrotoxicity has been reported in patients that fluconazole and tacrolimus were administered concurrently.

Theophylline:
In an interaction study with placebo control, use of fluconazole 200 mg for 14 days created a decrease of 18% in the mean plasma clearance of theophylline. The theophylline toxicity signs must be followed up during fluconazole intake in patients using high dosages of theophylline and under the risk of theophylline toxicity, and therapy must be changed accordingly in case of development of toxicity signs.

Vinca alkaloids:
Although not have been investigated, fluconazole can increase the plasma levels of vinca alkaloids (e.g. vincristine and vinblastin) and can cause neurotoxicity probably through its inhibitor effects on CYP3A4.

Vitamin A:
According to a case report on a patient receiving combination therapy with all-trans-retinoid acid (acid form of vitamin A) and fluconazole, the adverse effects on the central nervous system (CNS) developed in the form of pseudotumor cerebri; these effects disappeared after stopping fluconazole therapy. This combination can be used; however, the incidence of adverse effects on CNS must be taken into consideration.

Zidovudine:
Two kinetic studies were resulted in increased zidovudine levels, very probably because of decreased transformation of zidovudine into its major metabolites. In a study, the zidovudine levels before and after 200 mg fluconazole intake for 15 days were determined in patients with AIDS or ARC (period before AIDS). A significant increase of 20% was observed in the area under the curve (UAC) value of zidovudine. In a randomized, 2-period, 2-treatment, crosswise study, zidovudine levels were measured in patients infected with HIV. Patients received 200 mg zidovudine either with 400 mg fluconazole for 7 days with intervals of 21 days, or 200 mg zidovudine every 8 hours without fluconazole. The C_{max} and area under the curve (UAC) values of zidovudine were increased by 84% and 74%, respectively, when administered concurrently with fluconazole. Because of the decrease by about 45% in oral zidovudine clearance, the half life of zidovudine has been increased by 128% following the combination therapy with fluconazole. Patients receiving this combination must be followed up against the risk of adverse reactions related to zidovudine. Decreasing the dosage of zidovudine can be considered.

Interaction studies have shown that foods taken together with fluconazole, cimetidine, antacids or whole body irradiation after bone marrow transplantation do not result in clinically significant decreases in the absorption of fluconazole.

Since drug interactions with other drugs have not been carried out, doctors must be careful about any possible interactions.

Important information on special populations
Pediatric population:
Not available

4.6. Pregnancy and lactation

General advice
Pregnancy category:D

Women with child-bearing potential / Contraception
SELFLEKS FLUKOSEL should not be used in women with childbearing potential unless effective contraception is applied.

Pregnancy
Data obtained from hundreds of pregnant women treated with <200 mg/day doses of fluconazole administered as single or repeated dosages within the first three months of pregnancy had caused no adverse effects on the fetus. Prolonged use of fluconazole at a dose of 400-800 mg/day in the first trimester may increase the risk of congenital abnormalities. This risk has not been demonstrated by the treatment of single-dose, low-dose vaginal candidiasis infection.

There are no controlled studies carried out in sufficient numbers on pregnant women. Multiple congenital abnormalities were reported for the children of mothers who had used high dosages of fluconazole (400-800 mg/day) for 3 months or longer periods for the treatment of. The relationship between these effects and fluconazole is unclear. Adverse fetal effects were observed in animals only with high dosages related to maternal toxicity. No fetal effects were observed with dosages of 5 or 10 mg/kg; increases in the fetal anatomic variants (ribs in numbers greater than normal, dilation of the renal pelvis) and

delay of ossification were observed with dosages of 25, 50 mg/kg or over. Embryo lethality in rats have increased in dosages ranging between 80 mg/kg (approximately 20-60 folds of the dosage recommended for humans) to 320 mg/kg; fetal abnormalities included undulated ribs, cleft palate and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats, and can be the result of estrogen decrease during pregnancy, organogenesis and labor. Except for the serious or potentially life-threatening fungal infections or where the expected benefits will overcome the potential risk on fetus, use during pregnancy must be avoided.

Lactation

Fluconazole is present in breast milk in concentrations similar to plasma. Therefore, use in lactating mothers is not recommended.

Fertility

Reproductive toxicity

No fetal effects were seen in dosages between 5 and 10 mg/kg; increases in the fetal anatomic variants (ribs in numbers greater than normal, dilation of the renal pelvis) and delay of ossification were observed with dosages of 25, 50 mg/kg or over. Embryo lethality in rats have increased in dosages ranging between 80 mg/kg (approximately 20-60 folds of the dosage recommended for humans) to 320 mg/kg; fetal abnormalities included undulated ribs, cleft palate and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats, and can be the result of estrogen decrease during pregnancy, organogenesis and labor.

Fertility disorders

While labor was delayed for a short time after the oral administration of 20 mg/kg fluconazole, fertility of male and female rats was not affected from oral dosages of 5, 10 or 20 mg/kg/day or parenteral dosages of 5.25 or 75 mg/kg/day. In a perinatal study carried out on rats with intravenous dosages of 5, 20 and 40 mg/kg, dysostosis and prolongation of labor was observed in a few cases at 20 mg/kg (about 5-15 folds of the recommended human dosage) and 40 mg/kg dosages. These effects were not seen with 5 mg/kg dosage. These disorders at labor were reflected with the increased number of stillbirths and decrease in postnatal survival. These effects at birth are consistent with the estrogen reducing effect created with high dosages of fluconazole that are specific to species. A similar hormonal change was not seen in women that fluconazole was administered to. (See Section 5.1. Pharmacodynamic properties)

4.7. Effects on ability to drive and use machines

When driving or using machinery, it should be noted that occasional dizziness or seizures may occur.

4.8. Undesirable effects

Fluconazole is generally tolerated well.

Renal and hematologic functional changes and hepatic abnormalities (See: Section 4.4

Special warnings and precautions for use) have been observed during the treatment both with fluconazole and comparison drugs in some diseases, particularly in those with serious primary diseases including AIDS or cancer; however, the clinical significance of these and their relation with the treatment are unclear. The adverse effects are listed according to the categories given below:

Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10.000 and <1/1000), very rare (<1/10.000) and unknown (estimation based on the existing data is impossible).

Blood and the lymphatic system disorders
Rare: Agranulositosis, leukopenia, neutropenia and thrombocytopenia

Immune system disorders
Rare: Anaphylaxis (angioedema, facial edema, pruritus, urticaria included)

Metabolism and nutritional disorders
Rare: Hypercholesterolemia, hypertriglyceridemia, hypokalemia

Psychiatric disorders
Uncommon: Sleeplessness, sleepiness

Nervous system diseases
Common: Headache
Uncommon: Seizures, dizziness, paresthesias, lack of taste
Rare: Tremors

Ear and internal ear disorders
Uncommon: Vertigo

Cardiac disorders
Rare: QT prolongation, Torsades de pointes

Gastrointestinal disorders
Common: Abdominal pain, diarrhea, nausea and vomiting
Uncommon: Indigestion, flatulence and dry mouth

Hepatobiliary disorders
Common: High alkaline phosphatase levels, increase of aspartate aminotransferase, increase of blood alkaline phosphatase
Uncommon: Cholestasis, jaundice, bilirubin increase
Rare: Hepatic toxicity that can result in death rarely, hepatic insufficiency, hepatitis, hepatocellular necrosis, hepatocellular injury, jaundice

Cutaneous and subcutaneous disorders
Common: Rashes
Uncommon: Pruritus, urticaria, increase of sweating, drug eruptions

Rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute disseminated exanthamatous pustulous exfoliative skin diseases, facial edema, hair loss

Musculoskeletal disorders, connective tissue and bone disorders
Uncommon: Myalgia

General disorders and problems related to administration site
Uncommon: Fatigue, malaise, astenia, fever

Pediatric patients
The adverse event incidence and model and laboratory abnormalities recorded during pediatric clinical studies are comparable to those seen in adults.

Reporting of suspected adverse reactions
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Over-dosage cases with fluconazole have been reported: a 42-year old patient infected with HIV had taken 8200 mg fluconazole and developed hallucinations, and the patient displayed paranoid behaviors. The patient was hospitalized, and his/her condition returned to normal within 48 hours.

Symptomatic treatment (including supportive measures and gastric lavage if required) can suffice in case of over-dosage.

Fluconazole is largely excreted within urine; forced volume diuresis will probably increase the elimination rate. A hemodialysis séance of three hours will decrease the plasma level by 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : TRIAZOLE DERIVATIVE ANTIFUNGAL
ATC code : J02AC01

Fluconazole is a member of the triazole class antifungal agents, and is a strong and specific inhibitor of fungal sterol synthesis.

Fluconazole had displayed very little pharmacologic activity in many diverse animal studies. In mice, it caused some elongation in pentobarbital sleep period (p.o.) and in cats under anesthesia (IV) it caused increases in the mean arterial and left ventricular blood pressure and in heart rate. Inhibition of aromatase in the ova of rats occurred with high dosages.

Fluconazole administered both orally or intravenously is active in several fungal infection models in animals. It activity against opportunist mycoses has been shown to include systemic candidiasis in animals with immunosupression, infections related to *Cryptococcus neoformans* including the intracranial infections, and infections related to *Microsporum* and *Trichophyton* species. Apart from the above, activity of fluconazole in animal models for endemic mycoses have also been shown including *Blastomyces dermatitides*; *Coccidioides immitis* including intracranial infections and *Histoplasma capsulatum* infections in both normal and immunosuppressed animals.

Superinfection cases have been reported caused by Candida species other than *Candida albicans* that inherently are not sensitive for fluconazole (e.g. *Candida krusei*). Such cases can require alternative antifungal treatments.

Fluconazole is very specific for fungal CYP dependent enzymes. It has been shown that fluconazole 50 mg daily administered up to 28 days did not affect the plasma concentrations ot testosterone in males and steroid concentrations in females in fertile ages. Fluconazole in daily dosages of 200-400 mg did not have significant clinical effects on the endojen steroid levels or response stimulated with ACTH in the healthy male volunteers. Studies on the interaction with antipyrine have shown that single or repeated dosages of fluconazole 50 mg did not affect the metabolism of this substance.

Efficacy of fluconazole in tinea capitis was investigated in two randomized and controlled studies on 878 patients in total that griseofulvin was compared with fluconazole. Fluconazole administered in 6 mg/kg/day dosage for 6 weeks is not superior to griseofulvin administered in 11 mg/kg/day dosage for 6 weeks. In all the treatment groups, the general success rate at week 6 was low (fluconazole at week 6: 18.3%; fluconazole at week 3: 14.7%; griseofulvin: %17.7). These findings are not consistent with the natural course of the tinea capitis without treatment.

5.2 Pharmacokinetic properties

General properties

Absorption:

Pharmacokinetic properties of fluconazole after oral or intravenous administration resemble each other. Fluconazole well absorbed after oral administration and the plasma levels (and systemic bioavailability) will be higher than the 90% of the levels reached following intravenous administration. Oral absorption is not affected from simultaneous food intake. The peak plasma levels in fasting will be reached within 0.5 to 1.5 hours following the dosage, and plasma elimination half-life is about 30 hours. Plasma concentrations are proportional with dosage. The steady-state 90% after repeated once-daily dosages will be reached at days 4-5. The loading dosage administered as two-folds of the routing daily dosage ensures the plasma concentrations reach the 90% of the steady-state concentration in the second day.

Distribution:
The apparent distribution level is approximately equal to the total body fluids. Ratio of binding to plasma proteins is low (11-12%).

Fluconazole penetrates well into all the body fluids examined. The fluconazole levels in saliva and sputum resemble the levels in plasma. The fluconazole level in patients with fungal meningitis in CSF (cerebrospinal fluid) is approximately 80% of the corresponding plasma levels.

Fluconazole reaches high levels in skin, stratum corneum, epidermis-dermis and sweat glands that are above the serum concentrations. Fluconazole accumulates in stratum corneum. The fluconazole concentration with once-daily 50 mg dosage was 73 microgram/g after 12 days, and the concentration was still 5.8 microgram/g 7 days later than stopping the treatment. The concentration of fluconazole 150 mg administered once weekly in stratum corneum was 23.4 microgram/g at day 7, and was still 7.1 microgram/g 7 days later than the 2^{nd} dosage.

The fluconazole concentrations measured in fingernails of healthy individuals and patients 4 months later than 150 mg dosage administered once weekly were 4.05 microgram/g and 1.8 microgram/g, respectively, and were still at measurable levels 6 months later.

Biotransformation:
No evidences of circulating metabolites have been found.

Elimination:
The main excretion route is through the kidneys, and about 80% of the administered dosage is found unchanged in urine. Fluconazole clearance is proportional with the creatinine clearance.

The long plasma elimination half life is the basis for the treatment of vaginal candidiasis with one single dose, and treatment of all the other fungal infections it is indicated in with daily or weekly single dosages.

In a study, the concentrations were compared of an oral suspension in saliva and plasma administered by keeping one single dose of 100 mg in the mouth for 2 minutes and then rinsing. The maximum concentration of fluconazole in saliva 5 minutes later than swallowing the dosage was found as 182 folds of the maximum concentration of fluconazole in saliva measured 4 hours after swallowing the dosage. The saliva concentrations measured 4 hours later were similar to each other. The UAC in saliva (0-96) was significantly higher for the suspension than the capsule. There were no significant differences between the elimination from the saliva and the plasma pharmacokinetic parameters between the two formulations.

Linearity/Nonlinearity:

Not available.

Characteristics of patients

Pediatric pharmacokinetics:
The following pharmacokinetic data have reported for children:

Age group	Dosage (mg/kg)	Half-life(hour)	UAC (mcg.hour/mL)
11 days -11 months	Single dosage –IV, 3 mg/kg	23	110.1
9 months- 13 years	Single dosage –Oral, 2mg/kg	25.0	94.7
9 months- 13 years	Single dosage –Oral, 8mg/kg	19.5	362.5
5 years – 15 years	Multiple dosages – IV, 2 mg/kg	17.4*	67.4*
5 years – 15 years	Multiple dosages – IV, 4 mg/kg	15.2*	139.1*
5 years – 15 years	Multiple dosages – IV, 8 mg/kg	17.6*	196.7*
Mean 7 years	Multiple dosages –Oral, 3 mg/kg	15.5	41.6

* Shows the data of the last day

For the premature newborns (gestational age about 28 weeks) intravenous fluconazole was administered in 6 mg/kg dosage, when the premature newborns were in the intensive care unit, every three days and maximum for five days. The mean half-life is 74 hours at day one (range: 44-185), it decreases gradually and reaches to mean 53 hours at day 7 (range: 30-131) and to 47 hours at day 13 (range: 27-68).

The area under the curve was 271 mcg.hour/mL at day 1 (range: 173-385), and increased to mean 490 mcg.hour/mL at day 7 (range: 292-734), then decreased to mean 360 mcg.hour/mL (range: 167 – 566) at day 13.

The distribution volume at day 1 is 1183 mL/kg (range: 1070 – 1470), and gradually increases to reach 1184 mL/kg (range 510 – 2130) and at day 7 and 1328 mL/kg (range 1040-1680) at day 13.

Pharmacokinetics in the elderly:

In a pharmacokinetic study carried out on 22 subjects, one single dose of fluconazole of 50 mg was applied to patients 65 years old or older. Ten of these patients used also diuretics. C_{max} value was 1.54 microgram/mL, and C_{max} was reached 1.3 hours later than the administration. The mean UAC was 76.4 ± 20.3 microgram.hour/mL, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values were higher than the comparable values reported for healthy young male volunteers. Concurrent administration of diuretics did not change the UAC and C_{max} values significantly. Furthermore, the creatinine clearance kreatinin (74 mL/min), percentage of the unchanged drug in urine (0-24 hours, 22%) and the estimated fluconazole renal clearance (0.124 mL/min/kg) in the elderly population were found lower as compared to the same in young volunteers. Therefore, the changes in the fluconazole excretion seen in the elderly population are related to the low renal functions in this group. When plot showing creatinine clearance vs. the terminal elimination half-life in each subject is compared to a plot showing the estimated half-life vs. creatinine clearance in healthy volunteers and

patients with renal failure in various levels are compared, the estimated half-life vs. creatinine clearance in 21 patients out of 22 was found within 95% confidence interval. These results are consistent with the hypothesis that the pharmacokinetic parameter values in the elderly population as compared to the healthy young male population is related to the decrease in renal functions in the elderly population, as expected.

5.3 Preclinical safety data

Carcinogenesis
Fluconazole gave no evidences of carcinogenic potential in mice and rats in dosages of 2.5, 5 or 10 mg/kg/day (approx. 2-7 folds of the recommended dosage for humans) administered for 24 months. The incidence of hepatocellular adenoma increased in male rats that fluconazole was administered for 5 and 10 mg/kg/day dosages.

Mutagenesis
Fluconazole, metabolically active or inactive, gave negative results in the mutagenicity tests carried out on 4 strains of *S. typhimurium* and on mouse lymphoma L5178Y system. *In vivo* (bone marrow cells of muridae after oral fluconazole administration) and *in vitro* (human lymphocytes exposed to 1000 microgram/mL fluconazole) cytogenetic studies have revealed to evidences of chromosomal mutation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Water for injection

6.2 Incompatibilities
There are no known specific incompatibilities.
SELFLEKS FLUKOSEL intravenous infusion is compatible with the following administration fluids.

a) 20% Dextrose
b) Ringer solution
c) Hartmann solution
d) Potassium chloride in dextrose
e) 4.2% Sodium bicarbonate
f) Aminofusin
g) Physiologic Saline Water

SELFLEKS FLUKOSEL can be given in one of the solutions given above through any IV infusion set. Although no specific incompatibility has been observed, it is not recommended to mix the infusion fluids with any other drug.
It should be used immediately after dilution.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at room temperature below 25°C, in original packaging.
Do not use if the solution is not clear, contains particulates, or if the bag is damaged. The rest of the solution, some of which have been used, is not used again.

6.5 Nature and contents of container
100 mL solution in PVC bag.

6.6 Instructions for use and handling and disposal
Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

2016/448

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.05.2016
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

USER INFORMATION

Parenteral preparation products before use, the solution and packaging should be checked to see if they contain as many particulates as permitted and if the colour is impaired (see precautions).

Do not use products that are not clear and unpacked.

To open: tear the outer packaging from the top and remove the solution container. Some opacity can be seen on the plastic due to the absorption of moisture during the sterilization process. This is normal and does not affect the quality and reliability of the solution. Opacity will disappear over time.

Preparation for administration: (use aseptic technique)

1- Turn off the current control lock (clamp) of the administration set.
2- Remove the lid from the exit hole under the medicine bag.
3- Insert the needle of the administration set into the hole until the set is firmly seated.
4- Hang the bag on the suspension.
5- Tighten and release the chamber where the drop flows to ensure smooth fluid flow in the chamber.
6- Open the Flow Control Lock and remove the air from the set. Close the lock.
7- Connect the set to the venipuncture device. If the serum is not flowing, adjust the venipuncture.
8- Adjust administration speed with Flow Control Lock.

ATTENTION:
DO NOT USE FLEXIBLE BAGS IN MULTIPLE CONNECTIONS.
FOR SINGLE-DOSE USE.
I.V. USE
DO NOT ADD ADDITIVES TO THIS SOLUTION.
USE ONLY CLEAR SOLUTION AND UNOPENED PACKAGE.