SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUKODEKS 2 mg/ml Solution for I.V. Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:	**mg / ml**
Fluconazole	2 mg

100 ml solution contains 200 mg fluconazole, 200 ml solution contains 400 mg fluconazole.

Excipients:	
Dextrose anhydrous	50 mg
Water for injection	completed to 1.000 mL

For excipients see 6.1.

3. PHARMACEUTICAL FORM

FLUKODEKS sterile and apyrogen solution for intravenous infusion.

FLUKODEKS is a clear, colorless solution with a pH between 3.5 and 6.5.

4. CLINICAL PROPERTIES

4.1. Therapeutical 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.

FLUKODEKS 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

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 Broncho pulmonary infections, candiduria, mucocutaneous candidiasis etc., is 50-100mg 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 50-400mg 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.

Administration Route:

FLUKODEKS solution for infusion is administered intravenously.

Fluconazole is given both orally and intravenously as an infusion rate of 10 ml per minute. The route of administration depends on the clinical condition of the patient. There is no need to change the daily dose when passing from the intravenous route to the oral route or vice versa. FLUKODEKS infusion form is formulated in 5% dextrose solution and every 100 ml contains 5 g dextrose. FLUKODEKS intravenous infusion is compatible with the following application fluids.

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

FLUKODEKS 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 related to 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 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 séance

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 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.

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

FLUKODEKS 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 application of drugs including cisapride, astemizole, pimozide and quinidine, which are known to extend the QT interval and metabolized with CYP3 A4 enzyme is contra-indicated in patients taking fluconazole (See: Sections 4.4 and 4.5).

4.4. Special warnings and 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 FLUKODEKS 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 dosages of FLUKODEKS. 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: Sections 4.3 and 4.5).

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 elongation has not been determined fully, fluconazole must be used carefully in patients with potential pro-arrhythmic conditions:
• Congenital or acquired documented QT elongation
• Cardiomyopathy – particularly together with cardiac insufficiency
• Sinus bradichardia
• Existing symptomatic arrhythmias
• Concurrent use of drugs not metabolized with CY34A, but known to extend the QT interval
• Electrolyte imbalances including hypokalemia or hypomagnesemia

Fluconazole must be used with care in patients with renal dysfunction (See: Section 4.2).

Fluconazole is a potent inhibitor of CYP2C9, and medium inhibitor of CYP3A4. Patients treated concurrently with fluconazolele and drugs with narrow therapeutical windows and metabolized with CYP2C9 and CYP3A4 enzymes must be followed-up (See: Section 4. 5).

This medicinal product contains dextrose. Caution should be exercised in patients with dextrose intake, such as patients with kidney failure and diabetes mellitus. Solutions containing dextrose should be administered with caution to patients with known diabetes mellitus or those with

subclinical diabetes and carbohydrate intolerance for any reason. Solutions containing dextrose can be contraindicated in people with hypersensitivity to corn or corn products.

4.5. Interactions with other medical products and other forms of interaction

Its use together with the following products is contraindicated:

Cisapride:

Some cardiac events including torsade 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 contra-indicated (See: Section 4.3).

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.). 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).

Astemizole:

Concurrent administration of fluconazole with astemizole can decrease the clearance of astemizole. The increase of plasma concentrations of astemizole can cause QT extension, and rarely, occurrence of torsade de pointes. Concurrent use of fluconazole and astemizole is contra-indicated (See: Section 4.3).

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 elongation of QT and occurrence of torsade de pointes rarely. Administration of fluconazole concurrently with pimozide is contra-indicated (See: Section 4.3.).

Use together with the medical products is not recommended:

Erythromycin:
The concurrent use of fluconazole and erythromycin has the potential of causing cardiotoxicity (elongated QT interval, torsades de pointes) 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 cytochrome P450 (CYP) 2C9 iso-enzyme and medium-level inhibitor of CYP3A4. 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 followed-up 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.).

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 might 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. Dosage of amitriptyline/nortriptyline must be adjusted is required.

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 (with short-term effects):
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 followed-up 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 /effect.

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 follow-up is recommended against adverse events.

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. Follow-up 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, 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-CoA 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 followed as regards the symptoms of myopathy and rhamdomyolysis symptoms, and creatinine kinase must be monitored. HMG-CoA 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 EAA 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), whşch 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:
Fluconazole 50 mg daily 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 followed-up carefully.

Sakinavir:
Fluconazole increases the UAC value of sakinavir by about 50% and Cmax 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 lives in serum are elongated. Fluconazole can be used together with oral sulfonylurea drugs in diabetic patients; however, the possibility of hypoglycemic episodes must 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 pseudo tumor 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 (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
Pregnancy category: C

Women with potential of giving birth /Contraception
FLUKODEKS must not be used in women with the potential of giving birth unless effective contraception methods are used.

Pregnancy period

Data obtained from hundreds of pregnant women treated with <200 mg/dosages of fluconazole administered as single or repeated dosages within the first three months of pregnancy had caused no adverse effects on the fetus.

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 25mg/kg, 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 period

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

Reproductive capability/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 25mg/kg, 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 elongation 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.).

4.7. Effects on ability to drive and use machines

It must be taken into consideration that vertigo or seizures can occur when driving or using machines.

4.8. Undesirable effects
Fluconazole is generally tolerated well.

Renal and hematologic functional changes and hepatic abnormalities (See: Section 4.4) 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 lymphatic system disorders
Rare: Agranulositosis, leukopenia, neutropenia and thrombocytopenia

Disorders of the immune system

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 elongation, torsade 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.

4.9. Overdosage

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 periods of three hours will decrease the plasma level by 50%.

5. PHARMACOLOGIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacoterapeutical group: Triazole derivatives
ATC code: J02AC

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 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.

Super-infection 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 cytochrome P-450 dependent enzymes. It has been shown that fluconazole 50 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/Nonlinear status:

Not Applicable

Characteristics of patients

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

Age group	**Dosage (mg/kg)**	**Half-life**	**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 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 population:

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 application. 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. Preclinic 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 PROPERTIES

6.1. List of excipients

Dextrose anhydrous (parenteral quality)
Water for injection

6.2. Incompatibilities

There are no known specific incompatibilities.

FLUKODEKS intravenous infusion solution is compatible with the following administration fluids.

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

FLUKODEKS 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.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Keep at room temperature under 25°C.

6.5. Nature and contents of container

FLUKODEKS 2 mg / ml Solution for I.V. Infusion is offered in 100 and 200 ml PP bags. It has 2 forms with and without set.

6.6. Special precautions for disposal

The unused products and waste materials must be destructed according to the "Regulation Related to the Control of Medical Wastes" and the "Regulation Related to the Control of Packaging Materials and Packaging Wastes".

Instruction manual

The solution should be checked before use.
Application is done intravenously with sterile pyrogen sets.

Only clear, particle-free and intact packaging integrity products should be used.

Application should be started as soon as possible after the application set is attached to the product.

Serial connections with other infusion fluids should not be made to prevent an air embolism that may occur due to residual air in the bag.

The solution should be applied using a aseptic technique through a sterile administration set. Liquid must be passed through the application set before use to prevent air from entering the system.

Additional drugs can be added before and during infusion with the help of a needle from the injection tip in aseptic conditions. The isotonicity of the resulting product must be determined before parenteral administration.

The added drug must be completely mixed with the solution before applying to the patient. Solutions containing additional drugs should be used immediately after the drug is added; should not be stored for use later.

Addition of the drug to the solution or wrong application technique may cause fever reaction due to pyrogen contamination to the product. In the event of an adverse reaction, the infusion should be stopped immediately.
It is disposable.

Partially used solutions should not be stored.
Partially used bags should not be reconnected to the systems applied to the patient.

To open:
1. Check the integrity of the outer packaging and for leaks; do not use if the packaging is damaged.
2. Tear open the protective outer packaging.
3. Tightly check whether the bag in the protective packaging is intact. Check that the solution in the bag is clear and free from foreign matter.

Application preparations:
1. Hang the bag.
2. Remove the protective cap on the application tip.
3. Insert the spike of the application set firmly into the application tip.
4. The instructions for use of the set should be followed to apply the solution to the patient.

Adding additional medication:
Caution: As with all parenteral solutions, all substances to be added to the product must be compatible with the product. If additions will be made to the product, compatibility should be checked in the final mixture before applying to the patient.

Adding medication before application
1. The drug delivery tip is disinfected.
2. The drug to be added is added to the bag with a 19-22 gauge needle with a syringe.

3. The solution and the medication added are thoroughly mixed. In dense drugs such as potassium chloride, it is ensured that the bag is mixed by tapping the application outlet in the up position.
Caution: Bags with additional medication should not be stored.

Adding medication during application
1. The clamp of the set is closed.
2. The drug delivery tip is disinfected.
3. The drug to be added is applied through the injector tip with a 19-22 gauge needle.
4. The solution is removed from the rack and turned over.
5. While in this position, the application exit of the bag and the injection inlet are tapped gently to mix the solution and additional drug.
6. By opening the bag, the clamp is opened and the application is continued.

7. MARKETING AUTHORISATION HOLDER

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