TRIFLUCAN® I.V.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIFLUCAN® I.V.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg of fluconazole.

Excipient(s) with known effect:
Each ml contains 9 mg sodium chloride (equivalent to 0.154 mmol sodium) (see section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless solution with no visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole is indicated in the following fungal infections (see section 5.1).

Fluconazole is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- Invasive candidiasis.
- Mucosal candidiasis (including oropharyngeal candidiasis, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis).
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.

Fluconazole is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Haematopoetic Stem Cell Transplantation (see section 5.1)).

Fluconazole is indicated in term newborn infants, infants, toddlers, children and adolescents aged from 0 to 17 years old**:**

Fluconazole is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4).

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

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration

Posology

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Adults:

Indications		Posology	Duration of treatment
Cryptococcosis	- Treatment of cryptococcal meningitis	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg once daily	Usually at least 6 to 8 weeks. In life-threatening infections the daily dose can be increased to 800 mg.
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence	200 mg once daily	Indefinitely at a daily dose of 200 mg
Coccidioidomycosis		200 mg to 400 mg once daily	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease.
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg once daily	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg once daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function.

	- Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg once daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function.
	- Candiduria	200 mg to 400 mg once daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
	- Chronic atrophic candidiasis	50 mg once daily	14 days
	- Chronic mucocutaneous candidiasis	50 mg to 100 mg once daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromisation and infection.
Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse	- Oropharyngeal candidiasis	100 mg to 200 mg once daily or 200 mg 3 times per week.	An indefinite period for patients with chronic immune suppression.
	- Oesophageal candidiasis	100 mg to 200 mg once daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression.
Prophylaxis of candidal infections		200 mg to 400 mg once daily	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm^3.

Special populations

Elderly
Dosage should be adjusted based on the renal function (see "*Renal impairment*").

Renal impairment
Fluconazole is predominantly excreted in the urine as unchanged active substance. No adjustments in single-dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine clearance (ml/min)	**Percent of recommended dose**
>50	100%
≤50 (no haemodialysis)	50%
Haemodialysis	100% after each haemodialysis

Patients on haemodialysis should receive 100% of the recommended dose after each haemodialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance.

Hepatic impairment
Limited data are available in patients with hepatic impairment; therefore fluconazole should be administered with caution to patients with liver dysfunction (see sections 4.4 and 4.8).

Paediatric population

A maximum dose of 400 mg daily should not be exceeded in paediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole is administered as a single daily dose.

For paediatric patients with impaired renal function, see dosing in "*Renal impairment*". The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for "Term newborn infants" who often exhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

Indication	**Posology**	**Recommendations**
- Mucosal candidiasis	Initial dose: 6 mg/kg Subsequent dose: 3 mg/kg once daily	Initial dose may be used on the first day to achieve steady state levels more rapidly
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg once daily	Depending on the severity of the disease
- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 6 mg/kg once daily	Depending on the severity of the disease
- Prophylaxis of *Candida* in immunocompromised patients	Dose: 3 to 12 mg/kg once daily	Depending on the extent and duration of the induced neutropenia (see Adults posology)

Adolescents (from 12 to 17 years old):
Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Term newborn infants (0 to 27 days):
Neonates excrete fluconazole slowly.
There are few pharmacokinetic data to support this posology in term newborn infants (see section 5.2).

Age group	Posology	Recommendations
Term newborn infants (0 to 14 days)	The same mg/kg dose as for infants, toddlers and children should be given every 72 hours	A maximum dose of 12 mg/kg every 72 hours should not be exceeded
Term newborn infants (from 15 to 27 days)	The same mg/kg dose as for infants, toddlers and children should be given every 48 hours	A maximum dose of 12 mg/kg every 48 hours should not be exceeded

Method of administration
Fluconazole may be administered either orally or by intravenous infusion (Solution for Infusion), the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or *vice versa*, there is no need to change the daily dose.
The physician should prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. The capsule formulation is not adapted for use in infants and small children. Oral liquid formulations of fluconazole are available that are more suitable in this population.

Intravenous infusion should be administrated at a rate not exceeding 10 ml/minute.
Triflucan I.V. is formulated in sodium chloride 9 mg/ml (0.9%) solution for infusion, each 200 mg (100 ml bottle) containing 15 mmol each of Na^+ and $C1^-$. Because Triflucan I.V. is available as a dilute sodium chloride solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

For instruction on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

~~Hypersensitivity to the active substance, to related azole substances, or to any of the excipients listed in section 6.1.~~

~~Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4, such as cisapride, astemizole, pimozide, quinidine, and erythromycin, is contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).~~

TRIFLUCAN® I.V. (fluconazole) is contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients. There is no information regarding cross hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing TRIFLUCAN® I.V. to patients with hypersensitivity to other azoles. Coadministration of other drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as erythromycin, pimozide, and quinidine are contraindicated in patients receiving fluconazole. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies and PRECAUTIONS.)

4.4 ~~Special w~~Warnings ~~and precautions for use~~

~~Tinea capitis~~
~~Fluconazole has been studied for treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Triflucan I.V. should not be used for *tinea capitis*.~~

~~Cryptococcosis~~
~~The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.~~

~~Deep endemic mycoses~~
~~The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as *paracoccidioidomycosis, lymphocutaneous sporotrichosis* and *histoplasmosis* is limited, which prevents specific dosing recommendations.~~

~~Renal system~~
~~Fluconazole should be administered with caution to patients with renal dysfunction (see section 4.2).~~

~~Adrenal insufficiency~~
~~Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with prednisone, see section 4.5 **'The effect of fluconazole on other medicinal products'**.~~

~~Hepatobiliary system~~
~~Fluconazole should be administered with caution to patients with liver dysfunction.~~

~~Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.~~

~~Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.~~
~~The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.~~

~~Cardiovascular system~~
~~Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (I_{kr}). The QT prolongation caused by~~

~~other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. During post-marketing surveillance, there have been very rare cases of QT prolongation and *torsades de pointes* in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular arrhythmias and *torsades de pointes*.~~

~~Fluconazole should be administered with caution to patients with potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 is contraindicated (see sections 4.3 and 4.5).~~

~~Halofantrine~~
~~Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended (see section 4.5).~~

~~Dermatological reactions~~
~~Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.~~

~~Hypersensitivity~~
~~In rare cases anaphylaxis has been reported (see section 4.3).~~

~~Cytochrome P450~~
~~Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Fluconazole-treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).~~

~~Terfenadine~~
~~The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).~~

~~Candidiasis~~
~~Studies have shown an increasing prevalence of infections with *Candida* species other than *C. albicans*. These are often inherently resistant (e.g. *C. krusei* and *C. auris*) or show reduced susceptibility to fluconazole (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various *Candida* species to fluconazole.~~

~~Excipients~~
~~This medicinal product contains 88.5 mg sodium per 25 ml, equivalent to 4.4% of the WHO recommended maximum daily intake of 2g sodium for an adult.~~

~~The maximum daily dose of this product is equivalent to 71% of the WHO recommended maximum daily intake for sodium.~~

~~Triflucan I.V solution for infusion is considered high in sodium. This should be particularly taken into account when it is administered to patients on a low salt diet.~~

1) Hepatic injury: TRIFLUCAN® I.V. should be administered with caution to patients with liver dysfunction. TRIFLUCAN® I.V. has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of TRIFLUCAN® I.V. associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex, or age of the patient has been observed. TRIFLUCAN® I.V. hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during TRIFLUCAN® I.V. therapy should be monitored for the development of more severe hepatic injury. TRIFLUCAN® I.V. should be discontinued if clinical signs and symptoms consistent with liver disease develop that may be attributable to TRIFLUCAN® I.V..

(2) Anaphylaxis: In rare cases, anaphylaxis has been reported.

(3) Dermatologic: Exfoliative skin disorders during treatment with TRIFLUCAN® I.V. have been reported. Fatal outcomes have been reported in patients with serious underlying diseases. Patients with deep seated fungal infections who develop rashes during treatment with TRIFLUCAN® I.V. should be monitored closely and the drug discontinued if lesions progress. Fluconazole should be discontinued in patients treated for superficial fungal infection who develop a rash that may be attributed to fluconazole.

(4) Potential for fetal harm: There are no adequate and well-controlled clinical trials of TRIFLUCAN® I.V. in pregnant women. Case reports describe a pattern of distinct congenital anomalies in infants exposed in utero to high dose maternal fluconazole (400 to 800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. If TRIFLUCAN® I.V. is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with TRIFLUCAN® I.V. 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials. (See PRECAUTIONS: Pregnancy.)

PRECAUTIONS

General
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. (See PRECAUTIONS, Drug Interactions.) During post-marketing surveillance, there have been rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. Most of these reports involved seriously ill patients with multiple confounding risk factors, such as structural heart disease,

electrolyte abnormalities, and concomitant medications that may have been contributory. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and torsade de pointes.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsade de pointes) and consequently sudden heart death. This combination should be avoided.

Fluconazole should be administered with caution to patients with renal dysfunction.

Adrenal insufficiency has been reported in patients receiving azoles, including fluconazole. Reversible cases of adrenal insufficiency have been reported in patients receiving fluconazole.

When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or seizures may occur.

Drug Interactions:
(See CONTRAINDICATIONS.) Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Patients treated with TRIFLUCAN® I.V., who are also concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9 and CYP3A4, should be monitored for adverse reactions associated with the concomitantly administered drugs. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19, and CYP3A4 coadministered with fluconazole. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4 to 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole. Clinically or potentially significant drug interactions between TRIFLUCAN® I.V. and the following agents/classes have been observed and are described in greater detail below:

Abrocitinib: Drug interaction studies indicate that when coadministered with fluconazole (strong inhibitor of CYP2C19; moderate inhibitor of CYP2C9 and CYP3A4), the systemic exposure of abrocitinib and its active metabolites increased (See CLINICAL PHARMACOLOGY). Avoid concomitant use of abrocitinib with TRIFLUCAN® I.V.. Refer to the abrocitinib Prescribing Information for additional details.

Alfentanil: A study observed a reduction in clearance and distribution volume as well as prolongation of t½ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of fluconazole and amiodarone is necessary, notably with high dose fluconazole (800 mg).

Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5 Nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after 1 week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with Candida albicans, no interaction in intracranial infection with Cryptococcus neoformans, and antagonism of the two drugs in systemic infection with A. fumigatus. The clinical significance of results obtained in these studies is unknown.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil, and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg), the celecoxib Cmax and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

Coumarin type anticoagulants: Prothrombin time may be increased in patients receiving concomitant TRIFLUCAN® I.V. and coumarin type anticoagulants. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Careful monitoring of prothrombin time in patients receiving TRIFLUCAN® I.V. and coumarin type anticoagulants is recommended. Dose adjustment of warfarin may be necessary. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Cyclosporine: TRIFLUCAN® I.V. significantly increases cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving TRIFLUCAN® I.V. and cyclosporine. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.) This combination may be used by reducing the dosage of cyclosporine depending on cyclosporine concentration.

Fentanyl: One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomized crossover study with 12 healthy volunteers, it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolized through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected. Dose reduction of statins may be needed. Refer to the statin-specific prescribing information for details.

Hydrochlorothiazide: In a pharmacokinetic interaction study, coadministration of multiple dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.

Ibrutinib: Moderate inhibitors of CYP3A4 such as fluconazole may increase plasma ibrutinib concentrations and increase risk of adverse reactions associated with ibrutinib. If ibrutinib and fluconazole are concomitantly administered, reduce the dose of ibrutinib as instructed in ibrutinib prescribing information and the patient should be frequently monitored for any adverse reactions associated with ibrutinib.

Ivacaftor and fixed dose ivacaftor combinations (e.g., tezacaftor/ivacaftor and ivacaftor/tezacaftor/elexacaftor): Coadministration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3 fold. If used concomitantly with a moderate inhibitor of CYP3A4, such as fluconazole, a reduction in the dose of ivacaftor (or ivacaftor combination) is recommended as instructed in the ivacaftor (or ivacaftor combination) prescribing information.

Lemborexant: Concomitant administration of fluconazole increased lemborexant Cmax and AUC by approximately 1.6- and 4.2-fold, respectively which is expected to increase risk of adverse reactions, such as somnolence. Avoid concomitant use of TRIFLUCAN® I.V. with lemborexant.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin Il-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Lurasidone: Concomitant use of moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.

Methadone: Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The Cmax and AUC of flurbiprofen were increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S (+)-ibuprofen] were increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other non steroidal anti-inflammatory drugs (NSAIDs) that are metabolized by CYP2C9 (e.g., naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, reduce the dose of olaparib as instructed in the LYNPARZA® (Olaparib) Prescribing Information.

Oral contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Oral hypoglycemics: Clinically significant hypoglycemia may be precipitated by the use of TRIFLUCAN® I.V. with oral hypoglycemic agents; one fatality has been reported from hypoglycemia in association with combined TRIFLUCAN® I.V. and glyburide use. TRIFLUCAN® I.V. reduces the metabolism of tolbutamide, glyburide, and glipizide and increases the plasma concentration of these agents. When TRIFLUCAN® I.V. is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Phenytoin: TRIFLUCAN® I.V. increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving TRIFLUCAN® I.V. and phenytoin is recommended. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Pimozide: Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and pimozide is contraindicated.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a 3 month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Quinidine: Although not studied in vitro or in vivo, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and quinidine is contraindicated. (See CONTRAINDICATIONS.)

Rifabutin: There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and fluconazole

concomitantly should be carefully monitored. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Rifampin: Rifampin enhances the metabolism of concurrently administered TRIFLUCAN® I.V.. Depending on clinical circumstances, consideration should be given to increasing the dose of TRIFLUCAN® I.V. when it is administered with rifampin. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Saquinavir: Fluconazole increases the AUC of saquinavir by approximately 50%, Cmax by approximately 55%, and decreases the clearance of saquinavir by approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

Short-acting benzodiazepines: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If short-acting benzodiazepines, which are metabolized by the cytochrome P450 system, are concomitantly administered with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Theophylline: TRIFLUCAN® I.V. increases the serum concentrations of theophylline. Careful monitoring of serum theophylline concentrations in patients receiving TRIFLUCAN® I.V. and theophylline is recommended. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Tofacitinib: Systemic exposure to tofacitinib is increased when tofacitinib is coadministered with fluconazole. Reduce the dose of tofacitinib when given concomitantly with fluconazole (i.e., from 5 mg twice daily to 5 mg once daily as instructed in the XELJANZ® [tofacitinib] label). (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Triazolam: Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, Cmax by 20% to 32%, and increases t½ by 25% to 50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

Tolvaptan: Plasma exposure to tolvaptan is significantly increased (200% in AUC; 80% in Cmax) when tolvaptan, a CYP3A4 substrate, is coadministered with fluconazole, a moderate CYP3A4 inhibitor. This interaction may result in the risk of a significant increase in adverse reactions associated with tolvaptan, particularly significant diuresis, dehydration, and acute renal failure. If tolvaptan and fluconazole

are concomitantly administered, the tolvaptan dose should be reduced as instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case report in one patient receiving combination therapy with all trans retinoid acid (an acid form of vitamin A) and fluconazole, central nervous system (CNS) related undesirable effects have developed in the form of pseudotumor cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: Avoid concomitant administration of voriconazole and fluconazole. Monitoring for adverse events and toxicity related to voriconazole is recommended; especially, if voriconazole is started within 24 h after the last dose of fluconazole. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies.)

Zidovudine: Fluconazole increases the Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approximately 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.

Physicians should be aware that interaction studies with medications other than those listed in the CLINICAL PHARMACOLOGY section have not been conducted, but such interactions may occur.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5 mg/kg/day, 5 mg/kg/day, or 10 mg/kg/day (approximately 2 to 7 times the recommended human dose). Male rats treated with 5 mg/kg/day and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in four strains of S. typhimurium, and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000 mcg/mL) showed no evidence of chromosomal mutations.

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg or with parenteral doses of 5 mg/kg, 25 mg/kg, or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg PO. In an intravenous perinatal study in rats at 5 mg/kg, 20 mg/kg, and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg (approximately 5 to 15 times the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific estrogen lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole. (See CLINICAL PHARMACOLOGY.)

Pregnancy

Teratogenic Effects.

Potential for Fetal Harm: Use in pregnancy should be avoided except in patients with severe or potentially life threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. A few published case reports describe a pattern of distinct congenital anomalies in infants exposed in utero to high dose maternal fluconazole (400 to 800 mg/day) during most or all of the first trimester. These reported anomalies are similar to those seen in animal studies. Effective contraceptive measures should be considered in women of child-bearing potential who are being treated with TRIFLUCAN® I.V. 400 to 800 mg/day and should continue throughout the treatment period and for approximately 1 week (5 to 6 half lives) after the final dose. If TRIFLUCAN® I.V. is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. Spontaneous abortions and congenital abnormalities have been suggested as potential risks associated with 150 mg of fluconazole as a single or repeated dose in the first trimester of pregnancy based on retrospective epidemiological studies. There are no adequate and well controlled studies of TRIFLUCAN® I.V. in pregnant women. (See WARNINGS: Potential for Fetal Harm.)

Human Data

Case reports describe a distinctive and rare pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease. These effects are similar to those seen in animal studies.

Epidemiological studies suggest a potential risk of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester, but these epidemiological studies have limitations and these findings have not been confirmed in controlled clinical trials.

Animal Data

Fluconazole was administered orally to pregnant rabbits during organogenesis in two studies at doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg and at 5 mg/kg, 25 mg/kg, and 75 mg/kg, respectively. Maternal weight gain was impaired at all dose levels (approximately 0.25 to 4 times the 400 mg clinical dose based on body surface area [BSA] comparison), and abortions occurred at 75 mg/kg (approximately 4 times the 400 mg clinical dose based on BSA); no adverse fetal effects were observed.

In several studies in which pregnant rats received fluconazole orally during organogenesis, maternal weight gain was impaired and placental weights were increased at 25 mg/kg. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 to 320 mg/kg (approximately 2 to 8 times the 400 mg clinical dose based on BSA), embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate, and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis, and parturition.

Nursing Mothers

Fluconazole was present in low levels in breast milk following administration of a single 150 mg dose, based on data from a study in 10 breastfeeding women who temporarily or permanently discontinued breastfeeding 5 days to 19 months postpartum. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 mL/kg/day) based on the mean peak milk concentration

(2.61 mcg/mL [range: 1.57 to 3.65 mcg/mL] at 5.2 hours post dose) was 0.39 mg/kg/day, which is approximately 13% of the recommended pediatric dose for oropharyngeal candidiasis. (Labeled pediatric dose is 6 mg/kg/day on the first day followed by 3 mg/kg/day; estimated infant dose is 13% of 3 mg/kg/day maintenance dose). There are no data on fluconazole levels in milk after repeated use or after high-dose fluconazole. A published survey of 96 breastfeeding women who were treated with fluconazole 150 mg every other day (average of 7.3 capsules [range 1 to 29 capsules]) for lactation-associated candida of the breasts reported no serious adverse reactions in infants. Caution should be exercised when TRIFLUCAN® I.V. is administered to a nursing woman.

Pediatric Use

An open-label, randomized, controlled trial has shown TRIFLUCAN® I.V. to be effective in the treatment of oropharyngeal candidiasis in children 6 months to 13 years of age. (See CLINICAL STUDIES.)

The use of TRIFLUCAN® I.V. in children with cryptococcal meningitis, Candida esophagitis, or systemic Candida infections is supported by the efficacy shown for these indications in adults and by the results from several small noncomparative pediatric clinical studies. In addition, pharmacokinetic studies in children (See CLINICAL PHARMACOLOGY) have established a dose proportionality between children and adults. (See DOSAGE AND ADMINISTRATION.)

In a noncomparative study of children with serious systemic fungal infections, most of which were candidemia, the effectiveness of TRIFLUCAN® I.V. was similar to that reported for the treatment of candidemia in adults. Of 17 subjects with culture-confirmed candidemia, 11 of 14 (79%) with baseline symptoms (3 were asymptomatic) had a clinical cure; 13/15 (87%) of evaluable patients had a mycologic cure at the end of treatment but two of these patients relapsed at 10 and 18 days, respectively, following cessation of therapy.

The efficacy of TRIFLUCAN® I.V. for the suppression of cryptococcal meningitis was successful in 4 of 5 children treated in a compassionate-use study of fluconazole for the treatment of life threatening or serious mycosis. There is no information regarding the efficacy of fluconazole for primary treatment of cryptococcal meningitis in children.

The safety profile of TRIFLUCAN® I.V. in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1,616 days. (See ADVERSE REACTIONS.)

Efficacy of TRIFLUCAN® I.V. has not been established in infants less than 6 months of age. (See CLINICAL PHARMACOLOGY.) A small number of patients (29) ranging in age from 1 day to 6 months have been treated safely with TRIFLUCAN® I.V..

Geriatric Use

In non-AIDS patients, side effects possibly related to fluconazole treatment were reported in fewer patients aged 65 and older (9%, n =339) than for younger patients (14%, n=2240). However, there was no consistent difference between the older and younger patients with respect to individual side effects. Of the most frequently reported (>1%) side effects, rash, vomiting, and diarrhea occurred in greater proportions of older patients. Similar proportions of older patients (2.4%) and younger patients (1.5%) discontinued fluconazole therapy because of side effects. In post-marketing experience, spontaneous reports of anemia and acute renal failure were more frequent among patients 65 years of age or older than in those between 12 and 65 years of age. Because of the voluntary nature of the reports and the natural increase in the incidence of

anemia and renal failure in the elderly, it is however not possible to establish a causal relationship to drug exposure.

Controlled clinical trials of fluconazole did not include sufficient numbers of patients aged 65 and older to evaluate whether they respond differently from younger patients in each indication. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Fluconazole is primarily cleared by renal excretion as unchanged drug. Because elderly patients are more likely to have decreased renal function, care should be taken to adjust dose based on creatinine clearance. It may be useful to monitor renal function. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

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

~~*Concomitant use of the following other medicinal products is contraindicated:*~~

~~Cisapride: There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).~~

~~Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.~~

~~Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).~~

~~Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).~~

~~Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).~~

~~Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently, sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).~~

~~*Concomitant use of the following other medicinal products cannot be recommended:*~~

~~Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).~~

~~*Concomitant use that should be used with caution:*~~

~~Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of fluconazole and amiodarone is necessary, notably with high dose fluconazole (800 mg).~~

~~*Concomitant use of the following other medicinal products lead to precautions and dose adjustments:*~~

~~The effect of other medicinal products on fluconazole~~

~~Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and a 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.~~

~~Interaction studies have shown that when oral fluconazole is coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.~~

~~Hydrochlorothiazide: In a pharmacokinetic interaction study, coadministration of multiple dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.~~

~~The effect of fluconazole on other medicinal products~~

~~Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolised by CYP2C9, CYP2C19 and CYP3A4 coadministered with fluconazole. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).~~

~~Abrocitinib: Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If co-administered with fluconazole, adjust the dose of abrocitinib as instructed in the abrocitinib prescribing information.~~

~~Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers, the alfentanil AUC_{10} increased 2-fold, probably through inhibition of CYP3A4.~~
~~Dose adjustment of alfentanil may be necessary.~~

~~Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the~~

~~combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary.~~

~~Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.~~

~~Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin, the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole, the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.~~

~~Benzodiazepines (short-acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.~~

~~Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect.~~

~~Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolised by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.~~

~~Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg), the celecoxib C_{max} and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.~~

~~Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.~~

~~Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl-fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely~~

~~for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.~~

~~HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases (dose-dependent) when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.~~

~~Ibrutinib: Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib to 280 mg once daily (two capsules) for the duration of the inhibitor use and provide close clinical monitoring.~~

~~Ivacaftor (alone or combined with drugs in the same therapeutic class): Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.~~

~~Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.~~

~~Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):~~

~~Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.~~

~~Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.~~

~~Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.~~

~~Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.~~

~~Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-3174), which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.~~

~~Lurasidone: Moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.~~

~~Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.~~

~~Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.~~

~~Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.~~

~~Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC_{24} by 75% and C_{min} by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.~~

~~Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three-month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.~~

~~Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.~~

~~Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.~~

~~Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.~~

~~Theophylline: In a placebo-controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high-dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.~~

~~Tofacitinib: Exposure of tofacitinib is increased when tofacitinib is co-administered with medications that result in both moderate inhibition of CYP3A4 and strong inhibition of CYP2C19 (e.g., fluconazole). Therefore, it is recommended to reduce tofacitinib dose to 5 mg once daily when it is combined with these drugs.~~

~~Tolvaptan: Exposure to tolvaptan is significantly increased (200% in AUC; 80% in C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced as instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.~~

~~Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.~~

~~Vitamin A: Based on a case report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS-related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS-related undesirable effects should be borne in mind.~~

~~Voriconazole: (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse events is recommended if voriconazole is used sequentially after fluconazole.~~

~~Zidovudine: Fluconazole increases C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.~~

~~Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.~~

~~Oral contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.~~

~~4.6 Fertility, pregnancy and lactation~~

~~Pregnancy~~

~~An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.~~

~~Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤ 450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.~~

~~There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.~~

~~Studies in animals have shown reproductive toxicity (see section 5.3).~~

~~Before becoming pregnant a washout period of approximately 1 week (corresponding to 5-6 half-lives) is recommended after a single dose or discontinuation of a course of treatment (see section 5.2).~~

~~Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.~~

~~Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.~~

~~Breast-feeding~~

~~Fluconazole passes into breast milk to reach concentrations similar to those in plasma (see section 5.2). Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breast-feeding is not recommended after repeated use or after high dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for fluconazole and any potential adverse effects on the breast-fed child from fluconazole or from the underlying maternal condition.~~

~~Fertility~~

~~Fluconazole did not affect the fertility of male or female rats (see section 5.3).~~

~~4.7 Effects on ability to drive and use machines~~

~~No studies have been performed on the effects of fluconazole on the ability to drive or use machines.~~

~~Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking fluconazole and should be advised not to drive or operate machines if any of these symptoms occur.~~

ADVERSE REACTIONS

TRIFLUCAN® I.V. is generally well tolerated.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

In Patients Receiving Multiple Doses for Other Infections:
Sixteen percent of over 4000 patients treated with TRIFLUCAN® I.V. (fluconazole) in clinical trials of 7 days or more experienced adverse events. Treatment was discontinued in 1.5% of patients due to adverse clinical events and in 1.3% of patients due to laboratory test abnormalities.

Clinical adverse events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%); however, the patterns in HIV infected and non-HIV infected patients were similar. The proportions of patients discontinuing therapy due to clinical adverse events were similar in the two groups (1.5%).

The following treatment-related clinical adverse events occurred at an incidence of 1% or greater in 4048 patients receiving TRIFLUCAN® I.V. for 7 or more days in clinical trials: nausea 3.7%, headache 1.9%, skin rash 1.8%, vomiting 1.7%, abdominal pain 1.7%, and diarrhea 1.5%.

Hepato-biliary: In combined clinical trials and marketing experience, there have been rare cases of serious hepatic reactions during treatment with TRIFLUCAN® I.V.. (See **WARNINGS**.) The spectrum of these hepatic reactions has ranged from mild transient elevations in transaminases to clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities. Instances of fatal hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly AIDS or malignancy) and often while taking multiple concomitant medications. Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. In each of these cases, liver function returned to baseline on discontinuation of TRIFLUCAN® I.V..

In two comparative trials evaluating the efficacy of TRIFLUCAN® I.V. for the suppression of relapse of cryptococcal meningitis, a statistically significant increase was observed in median AST (SGOT) levels from a baseline value of 30 IU/L to 41 IU/L in one trial and 34 IU/L to 66 IU/L in the other. The overall rate of serum transaminase elevations of more than 8 times the upper limit of normal was approximately 1% in fluconazole-treated patients in clinical trials. These elevations occurred in patients with severe underlying disease, predominantly AIDS or malignancies, most of whom were receiving multiple concomitant medications, including many known to be hepatotoxic. The incidence of abnormally elevated serum transaminases was greater in patients taking TRIFLUCAN® I.V. concomitantly with one or more of the following medications: rifampin, phenytoin, isoniazid, valproic acid, or oral sulfonylurea hypoglycemic agents.

Post-Marketing Experience
In addition, the following adverse events have occurred during post-marketing experience.

Immunologic: In rare cases, anaphylaxis (including angioedema, face edema and pruritus) has been reported.

Body as a Whole: Asthenia, fatigue, fever, malaise.

Cardiovascular: QT prolongation, torsade de pointes. (See **PRECAUTIONS**.)

Central Nervous System: Seizures, dizziness.

Hematopoietic and *Lymphatic:* Leukopenia, including neutropenia and agranulocytosis, thrombocytopenia.

Metabolic: Hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Gastrointestinal: Cholestasis, dry mouth, hepatocellular damage, dyspepsia, vomiting.

Other Senses: Taste perversion.

Musculoskeletal System: myalgia.

Nervous System: Insomnia, paresthesia, somnolence, tremor, vertigo.

Skin and Appendages: Acute generalized exanthematous pustulosis, drug eruption including fixed drug eruption, increased sweating, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) (see **WARNINGS**), alopecia.

Adverse Reactions in Children:
The pattern and incidence of adverse events and laboratory abnormalities recorded during pediatric clinical trials are comparable to those seen in adults.

In Phase II/III clinical trials conducted in the United States and in Europe, 577 pediatric patients, ages 1 day to 17 years were treated with TRIFLUCAN® I.V. at doses up to 15 mg/kg/day for up to 1,616 days. Thirteen percent of children experienced treatment-related adverse events. The most commonly reported events were vomiting (5%), abdominal pain (3%), nausea (2%), and diarrhea (2%). Treatment was discontinued in 2.3% of patients due to adverse clinical events and in 1.4% of patients due to laboratory test abnormalities. The majority of treatment-related laboratory abnormalities were elevations of transaminases or alkaline phosphatase.

Percentage of Patients With Treatment-Related Side Effects		
Agents	**Fluconazole (N=577)**	**Comparative (N=451)**
With any side effect	13.0	9.3
Vomiting	5.4	5.1
Abdominal pain	2.8	1.6
Nausea	2.3	1.6
Diarrhea	2.1	2.2

~~4.8 Undesirable effects~~

~~Summary of safety profile:~~
~~Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section 4.4).~~

~~The most frequently (≥1/100 to <1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.~~

~~The following adverse reactions have been observed and reported during treatment with fluconazole with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).~~

~~System Organ Class~~	~~Common~~	~~Uncommon~~	~~Rare~~	~~Not Known~~
~~Blood and the lymphatic system disorders~~		~~Anaemia~~	~~Agranulocytosis, leukopenia, thrombocytopenia, neutropenia~~	
~~Immune system disorders~~			~~Anaphylaxis~~	
~~Metabolism and nutrition disorders~~		~~Decreased appetite~~	~~Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia~~	
~~Psychiatric disorders~~		~~Somnolence, insomnia~~		
~~Nervous system disorders~~	~~Headache~~	~~Seizures, paraesthesia, dizziness, taste perversion~~	~~Tremor~~	
~~Ear and labyrinth disorders~~		~~Vertigo~~		
~~Cardiac disorders~~			~~*Torsade de pointes* (see section 4.4), QT prolongation (see section 4.4)~~	
~~Gastrointestinal disorders~~	~~Abdominal pain, vomiting,~~	~~Constipation, dyspepsia,~~		

	~~diarrhoea, nausea~~	~~flatulence, dry mouth~~			
~~**Hepatobiliary disorders**~~	~~Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)~~	~~Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)~~	~~Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)~~		
~~**Skin and subcutaneous tissue disorders**~~	~~Rash (see section 4.4)~~	~~Drug eruption* (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating~~	~~Toxic epidermal necrolysis (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous pustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia~~	~~Drug reaction with eosinophilia and systemic symptoms (DRESS)~~	
~~**Musculoskeletal and connective tissue disorders**~~		~~Myalgia~~			
~~**General disorders and administration site conditions**~~		~~Fatigue, malaise, asthenia, fever~~			

~~* including Fixed Drug Eruption~~

~~Paediatric population~~
~~The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.~~

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

~~There have been reports of overdose with fluconazole. Hallucination and paranoid behaviour have been concomitantly reported.~~
~~In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.~~

~~Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemodialysis session decreases plasma levels by approximately 50%.~~

There have been reports of overdose with fluconazole accompanied by hallucination and paranoid behavior.

In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted.

Fluconazole is largely excreted in urine. A 3 hour hemodialysis session decreases plasma levels by approximately 50%.

In mice and rats receiving very high doses of fluconazole, clinical effects in both species included decreased motility and respiration, ptosis, lacrimation, salivation, urinary incontinence, loss of righting reflex, and cyanosis; death was sometimes preceded by clonic convulsions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

~~Mechanism of action~~
~~Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14-alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14-alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.~~

~~Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH-stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.~~

~~Susceptibility *in vitro:*~~
~~*In vitro*, fluconazole displays antifungal activity against clinically common *Candida* species (including *C. albicans, C. parapsilosis, C. tropicalis). C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole. The MICs and epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans*.~~
~~Fluconazole also exhibits activity *in vitro* against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatiditis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.~~

~~Pharmacokinetic/pharmacodynamic relationship~~
~~In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly, cure is less likely for infections caused by strains with a higher fluconazole MIC.~~

~~Mechanisms of resistance~~

~~*Candida* spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole, which impacts adversely efficacy *in vivo* and clinically.~~

~~In usually susceptible species of *Candida*, the most commonly encountered mechanism of resistance development involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutation, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways.~~

~~There have been reports of superinfection with *Candida* species other than *C. albicans*, which often have inherently reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g. *C. krusei*, *C. auris*). Such infections may require alternative antifungal therapy. The resistance mechanisms have not been completely elucidated in some intrinsically resistant (*C. krusei*) or emerging (*C. auris*) species of *Candida*.~~

~~EUCAST Breakpoints~~

~~Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST AFST (European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rationale document (2020) version 3; European Committee on Antimicrobial Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs, Version 10.0, valid from 2020-02-04). These have been divided into non-species related breakpoints, which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:~~

~~Antifungal~~	~~Species-related breakpoints (S≤/R>) in mg/L~~						~~Non-species related breakpoints[A] S≤/R> in mg/L~~
	~~*Candida albicans*~~	~~*Candida dubliniensis*~~	~~*Candida glabrata*~~	~~*Candida krusei*~~	~~*Candida parapsilosis*~~	~~*Candida tropicalis*~~	
~~Fluconazole~~	~~2/4~~	~~2/4~~	~~0.001*/16~~	~~--~~	~~2/4~~	~~2/4~~	~~2/4~~

~~S = Susceptible, R = Resistant~~

~~A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.~~

~~-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.~~

~~* = The entire *C. glabrata* is in the I category. MICs against *C. glabrata* should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. I - Susceptible, increased exposure: A microorganism is categorised as Susceptible, increased exposure when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.~~

~~5.2 Pharmacokinetic properties~~

~~The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route.~~

~~Absorption~~
~~After oral administration fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.~~

~~Distribution~~
~~The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).~~

~~Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.~~

~~High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.~~

~~Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and fluconazole was still measurable in nail samples 6 months after the end of therapy.~~

~~Biotransformation~~
~~Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a moderate inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also a strong inhibitor of the isozyme CYP2C19.~~

~~Elimination~~
~~Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.~~

~~The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.~~

~~Pharmacokinetics in renal impairment~~
~~In patients with severe renal insufficiency, (GFR< 20 ml/min) half-life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.~~

~~Pharmacokinetics during lactation~~
~~A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma~~

~~and breast milk for 48 hours following a single 150 mg dose of Diflucan~~TRIFLUCAN® I.V.~~. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.~~

~~Pharmacokinetics in children~~
~~Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies: 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.~~

~~After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.~~

~~Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.~~

~~Pharmacokinetics in elderly~~
~~A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter AUC or C_{max}. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 hr, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.~~

~~5.3 Preclinical safety data~~

~~Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.~~

~~Carcinogenesis~~

~~Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.~~

~~Mutagenesis~~
~~Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *Salmonella typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 µg/ml) showed no evidence of chromosomal mutations.~~

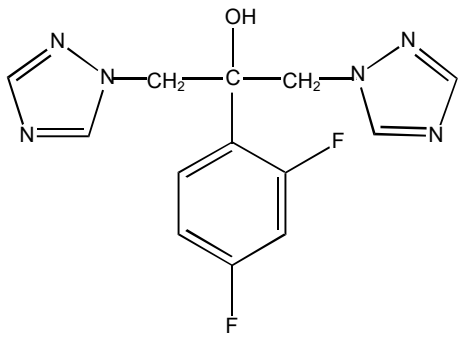
~~Reproductive toxicity~~
~~Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.~~

~~There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.~~
~~The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species-specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).~~

DESCRIPTION

TRIFLUCAN® I.V.® (fluconazole), the first of a new subclass of synthetic triazole antifungal agents, is available as a sterile solution for intravenous use in glass and in Viaflex® Plus plastic containers.

Fluconazole is designated chemically as 2,4-difluoro-α,α[1]-bis(1H-1,2,4-triazol-1-ylmethyl) benzyl alcohol with an empirical formula of $C_{13}H_{12}F_2N_6O$ and molecular weight of 306.3. The structural formula is:



Fluconazole is a white crystalline solid which is slightly soluble in water and saline.

TRIFLUCAN® I.V. Injection is an iso-osmotic, sterile, nonpyrogenic solution of fluconazole in a sodium chloride or dextrose diluent. Each mL contains 2 mg of fluconazole and 9 mg of sodium chloride or 56 mg of dextrose, hydrous. The pH ranges

from 4.0 to 8.0 in the sodium chloride diluent and from 3.5 to 6.5 in the dextrose diluent. Injection volumes of 100 mL and 200 mL are packaged in glass and in Viaflex® Plus plastic containers.

The Viaflex® Plus plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146® Plastic) (Viaflex and PL 146 are registered trademarks of Baxter International, Inc.). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexylphthalate (DEHP), up to 5 parts per million. However, the suitability of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration. Bioequivalence was established between the 100 mg tablet and both suspension strengths when administered as a single 200 mg dose.

Peak plasma concentrations (C_{max}) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20 to 50 hours) after oral administration.

In fasted normal volunteers, administration of a single oral 400 mg dose of TRIFLUCAN® I.V. (fluconazole) leads to a mean C_{max} of 6.72 mcg/mL (range: 4.12 to 8.08 mcg/mL) and after single oral doses of 50 to 400 mg, fluconazole plasma concentrations and area under the plasma concentration-time curve (AUC) are dose proportional.

Steady-state concentrations are reached within 5 to 10 days following oral doses of 50 to 400 mg given once daily. Administration of a loading dose (on Day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11 to 12%). Following either single- or multiple oral doses for up to 14 days, fluconazole penetrates into all body fluids studied (see table below). In normal volunteers, saliva concentrations of fluconazole were equal to or slightly greater than plasma concentrations regardless of dose, route, or duration of dosing. In patients with bronchiectasis, sputum concentrations of fluconazole following a single 150 mg oral dose were equal to plasma concentrations at both 4 and 24 hours post dose. In patients with fungal meningitis, fluconazole concentrations in the cerebrospinal fluid (CSF) are approximately 80% of the corresponding plasma concentrations.

A single oral 150 mg dose of fluconazole administered to 27 patients penetrated into vaginal tissue, resulting in tissue: plasma ratios ranging from 0.94 to 1.14 over the first 48 hours following dosing.

A single oral 150 mg dose of fluconazole administered to 14 patients penetrated into vaginal fluid, resulting in fluid: plasma ratios ranging from 0.36 to 0.71 over the first 72 hours following dosing.

Tissue or Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma Concentration*
Cerebrospinal fluid†	0.5-0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4-0.7

* Relative to concurrent concentrations in plasma in subjects with normal renal function.
† Independent of degree of meningeal inflammation.

In normal volunteers, fluconazole is cleared primarily by renal excretion, with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

The pharmacokinetics of fluconazole are markedly affected by reduction in renal function. There is an inverse relationship between the elimination half-life and creatinine clearance. The dose of TRIFLUCAN® I.V. may need to be reduced in patients with impaired renal function. (See **DOSAGE AND ADMINISTRATION**.) A 3-hour hemodialysis session decreases plasma concentrations by approximately 50%.

In normal volunteers, TRIFLUCAN® I.V. administration (doses ranging from 200 mg to 400 mg once daily for up to 14 days) was associated with small and inconsistent effects on testosterone concentrations, endogenous corticosteroid concentrations, and the adrenocorticotropic hormone (ACTH)-stimulated cortisol response.

Pharmacokinetics in Children

In children, the following pharmacokinetic data {Mean (%cv)} have been reported:

Age Studied	Dose (mg/kg)	Clearance (mL/min/kg)	Half-life (Hours)	C_{max} (mcg/mL)	Vdss (L/kg)
9 months-13 years	Single-Oral 2 mg/kg	0.40 (38%) N=14	25.0	2.9 (22%) N=16	—
9 months-13 years	Single-Oral 8 mg/kg	0.51 (60%) N=15	19.5	9.8 (20%) N=15	—
5-15 years	Multiple IV 2 mg/kg	0.49 (40%) N=4	17.4	5.5 (25%) N=5	0.722 (36%) N=4
5-15 years	Multiple IV 4 mg/kg	0.59 (64%) N=5	15.2	11.4 (44%) N=6	0.729 (33%) N=5
5-15 years	Multiple IV 8 mg/kg	0.66 (31%) N=7	17.6	14.1 (22%) N=8	1.069 (37%) N=7

Clearance corrected for body weight was not affected by age in these studies. Mean body clearance in adults is reported to be 0.23 (17%) mL/min/kg.

In premature newborns (gestational age 26 to 29 weeks), the mean (%cv) clearance within 36 hours of birth was 0.180 (35%, N=7) mL/min/kg, which increased with time to a mean of 0.218 (31%, N=9) mL/min/kg six days later and 0.333 (56%, N=4) mL/min/kg 12 days later. Similarly, the half-life was 73.6 hours, which decreased with time to a mean of 53.2 hours six days later and 46.6 hours 12 days later.

Pharmacokinetics in Elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 mcg/mL and occurred at 1.3 hours post dose. The mean AUC was 76.4 ± 20.3 mcg·h/mL, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter the AUC or C_{max}. In addition, creatinine clearance (74 mL/min), the percent of drug recovered unchanged in urine (0 to 24 hours, 22%), and the fluconazole renal clearance estimates (0.124 mL/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristic of this group. A plot of each subject's terminal elimination half-life versus creatinine clearance compared to the predicted half-life - creatinine clearance curve derived from normal subjects and subjects with varying degrees of renal insufficiency indicated that 21 of 22 subjects fell within the 95% confidence limit of the predicted half-life - creatinine clearance curves. These results are consistent with the hypothesis that higher values for the pharmacokinetic parameters observed in the elderly subjects compared to normal young male volunteers are due to the decreased kidney function that is expected in the elderly.

Drug Interaction Studies (See PRECAUTIONS, Drug Interactions)

Oral contraceptives: Oral contraceptives were administered as a single dose both before and after the oral administration of TRIFLUCAN® I.V. 50 mg once daily for 10 days in 10 healthy women. There was no significant difference in ethinyl estradiol or levonorgestrel AUC after the administration of 50 mg of TRIFLUCAN® I.V.. The mean increase in ethinyl estradiol AUC was 6% (range: –47 to 108%) and levonorgestrel AUC increased 17% (range: –33 to 141%).

In a second study, twenty-five normal females received daily doses of both 200 mg TRIFLUCAN® I.V. tablets or placebo for two, ten-day periods. The treatment cycles were one month apart with all subjects receiving TRIFLUCAN® I.V. during one cycle and placebo during the other. The order of study treatment was random. Single doses of an oral contraceptive tablet containing levonorgestrel and ethinyl estradiol were administered on the final treatment day (Day 10) of both cycles. Following administration of 200 mg of TRIFLUCAN® I.V., the mean percentage increase of AUC for levonorgestrel compared to placebo was 25% (range: –12 to 82%) and the mean percentage increase for ethinyl estradiol compared to placebo was 38% (range: –11 to 101%). Both of these increases were statistically significantly different from placebo.

A third study evaluated the potential interaction of once-weekly dosing of fluconazole 300 mg to 21 normal females taking an oral contraceptive containing ethinyl estradiol and norethindrone. In this placebo-controlled, double-blind, randomized, two-way crossover study carried out over three cycles of oral contraceptive treatment, fluconazole dosing resulted in small increases in the mean AUCs of ethinyl estradiol and norethindrone compared to similar placebo dosing. The mean AUCs of ethinyl estradiol and norethindrone increased by 24% (95% C.I. range: 18 to 31%) and 13% (95% C.I. range: 8 to 18%), respectively, relative to placebo. Fluconazole treatment did not cause a decrease in the ethinyl estradiol AUC of any individual subject in this study compared to placebo dosing. The individual AUC values of norethindrone decreased very slightly (<5%) in 3 of the 21 subjects after fluconazole treatment.

Cimetidine: TRIFLUCAN® I.V. 100 mg was administered as a single oral dose alone and two hours after a single dose of cimetidine 400 mg to six healthy male volunteers. After the administration of cimetidine, there was a significant decrease in fluconazole AUC and C_{max}. There was a mean ± SD decrease in fluconazole AUC of 13% ± 11% (range: –3.4 to –31%) and C_{max} decreased 19% ± 14% (range: –5 to –40%). However, the administration of cimetidine 600 mg to 900 mg intravenously over a four-hour period (from one hour before to 3 hours after a single oral dose of TRIFLUCAN® I.V. 200 mg) did not affect the bioavailability or pharmacokinetics of fluconazole in 24 healthy male volunteers.

Antacid: Administration of Maalox® (20 mL) to 14 normal male volunteers immediately prior to a single dose of TRIFLUCAN® I.V. 100 mg had no effect on the absorption or elimination of fluconazole.

Hydrochlorothiazide: Concomitant oral administration of 100 mg TRIFLUCAN® I.V. and 50 mg hydrochlorothiazide for 10 days in 13 normal volunteers resulted in a significant increase in fluconazole AUC and C_{max} compared to TRIFLUCAN® I.V. given alone. There was a mean ± SD increase in fluconazole AUC and C_{max} of 45% ± 31% (range: 19 to 114%) and 43% ± 31% (range: 19 to 122%), respectively.

These changes are attributed to a mean ± SD reduction in renal clearance of 30% ± 12% (range: –10 to –50%).

Rifampin: Administration of a single oral 200 mg dose of TRIFLUCAN® I.V. after 15 days of rifampin administered as 600 mg daily in eight healthy male volunteers resulted in a significant decrease in fluconazole AUC and a significant increase in apparent oral clearance of fluconazole. There was a mean ± SD reduction in fluconazole AUC of 23% ± 9% (range: –13 to –42%). Apparent oral clearance of fluconazole increased 32% ± 17% (range: 16 to 72%). Fluconazole half-life decreased from 33.4 ± 4.4 hours to 26.8 ± 3.9 hours. (See **PRECAUTIONS**.)

Warfarin: There was a significant increase in prothrombin time response (area under the prothrombin time-time curve) following a single dose of warfarin (15 mg) administered to 13 normal male volunteers following oral TRIFLUCAN® I.V. 200 mg administered daily for 14 days as compared to the administration of warfarin alone. There was a mean ± SD increase in the prothrombin time response (area under the prothrombin time-time curve) of 7% ± 4% (range: –2 to 13%). (See **PRECAUTIONS**.) Mean is based on data from 12 subjects as one of 13 subjects experienced a 2-fold increase in his prothrombin time response.

Phenytoin: Phenytoin AUC was determined after 4 days of phenytoin dosing (200 mg daily, orally for 3 days followed by 250 mg intravenously for one dose) both with and without the administration of fluconazole (oral TRIFLUCAN® I.V. 200 mg daily for 16 days) in 10 normal male volunteers. There was a significant increase in phenytoin AUC. The mean ± SD increase in phenytoin AUC was 88% ± 68% (range: 16 to 247%). The absolute magnitude of this interaction is unknown because of the intrinsically nonlinear disposition of phenytoin. (See **PRECAUTIONS**.)

Cyclosporine: Cyclosporine AUC and C_{max} were determined before and after the administration of fluconazole 200 mg daily for 14 days in eight renal transplant patients who had been on cyclosporine therapy for at least 6 months and on a stable cyclosporine dose for at least 6 weeks. There was a significant increase in cyclosporine AUC, C_{max}, C_{min} (24-hour concentration), and a significant reduction in apparent oral clearance following the administration of fluconazole. The mean ± SD increase in AUC was 92% ± 43% (range: 18 to 147%). The C_{max} increased 60% ± 48% (range: –5 to 133%). The C_{min} increased 157% ± 96% (range: 33 to 360%). The apparent oral clearance decreased 45% ± 15% (range: –15 to –60%). (See **PRECAUTIONS**.)

Zidovudine: Plasma zidovudine concentrations were determined on two occasions (before and following fluconazole 200 mg daily for 15 days) in 13 volunteers with AIDS or ARC who were on a stable zidovudine dose for at least two weeks. There was a significant increase in zidovudine AUC following the administration of fluconazole. The mean ± SD increase in AUC was 20% ± 32% (range: –27 to 104%). The metabolite, GZDV, to parent drug ratio significantly decreased after the administration of fluconazole, from 7.6 ± 3.6 to 5.7 ± 2.2.

Theophylline: The pharmacokinetics of theophylline were determined from a single intravenous dose of aminophylline (6 mg/kg) before and after the oral administration of fluconazole 200 mg daily for 14 days in 16 normal male volunteers. There were significant increases in theophylline AUC, C_{max}, and half-life with a corresponding decrease in clearance. The mean ± SD theophylline AUC increased 21% ± 16% (range:

–5 to 48%). The C_{max} increased 13% ± 17% (range: –13 to 40%). Theophylline clearance decreased 16% ± 11% (range: –32 to 5%). The half-life of theophylline increased from 6.6 ± 1.7 hours to 7.9 ± 1.5 hours. (See **PRECAUTIONS**.)

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of torsade de pointes. Coadministration of fluconazole and quinidine is contraindicated. (See **CONTRAINDICATIONS** and **PRECAUTIONS**.)

Oral hypoglycemics: The effects of fluconazole on the pharmacokinetics of the sulfonylurea oral hypoglycemic agents tolbutamide, glipizide, and glyburide were evaluated in three placebo-controlled studies in normal volunteers. All subjects received the sulfonylurea alone as a single dose and again as a single dose following the administration of TRIFLUCAN® I.V. 100 mg daily for 7 days. In these three studies, 22/46 (47.8%) of TRIFLUCAN® I.V.-treated patients and 9/22 (40.1%) of placebo-treated patients experienced symptoms consistent with hypoglycemia. (See **PRECAUTIONS**.)

Tolbutamide: In 13 normal male volunteers, there was significant increase in tolbutamide (500 mg single dose) AUC and C_{max} following the administration of fluconazole. There was a mean ± SD increase in tolbutamide AUC of 26% ± 9% (range: 12 to 39%). Tolbutamide C_{max} increased 11% ± 9% (range: –6 to 27%). (See **PRECAUTIONS**.)

Glipizide: The AUC and C_{max} of glipizide (2.5 mg single dose) were significantly increased following the administration of fluconazole in 13 normal male volunteers. There was a mean ± SD increase in AUC of 49% ± 13% (range: 27 to 73%) and an increase in C_{max} of 19% ± 23% (range: –11 to 79%). (See **PRECAUTIONS**.)

Glyburide: The AUC and C_{max} of glyburide (5 mg single dose) were significantly increased following the administration of fluconazole in 20 normal male volunteers. There was a mean ± SD increase in AUC of 44% ± 29% (range: –13 to 115%) and C_{max} increased 19% ± 19% (range: –23 to 62%). Five subjects required oral glucose following the ingestion of glyburide after 7 days of fluconazole administration. (See **PRECAUTIONS**.)

Rifabutin: There have been published reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. (See **PRECAUTIONS**.)

Tacrolimus: There have been published reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. (See **PRECAUTIONS**.)

Midazolam: The effect of fluconazole on the pharmacokinetics and pharmacodynamics of midazolam was examined in a randomized, cross-over study in 12 volunteers. In the study, subjects ingested placebo or 400 mg fluconazole on Day 1 followed by 200 mg daily from Day 2 to Day 6. In addition, a 7.5 mg dose of midazolam was orally ingested on the first day, 0.05 mg/kg was administered intravenously on the fourth day, and 7.5 mg orally on the sixth day. Fluconazole reduced the clearance of IV midazolam by

51%. On the first day of dosing, fluconazole increased the midazolam AUC and C_{max} by 259% and 150%, respectively. On the sixth day of dosing, fluconazole increased the midazolam AUC and C_{max} by 259% and 74%, respectively. The psychomotor effects of midazolam were significantly increased after oral administration of midazolam but not significantly affected following intravenous midazolam.

A second randomized, double-dummy, placebo-controlled, cross over study in three phases was performed to determine the effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. In each phase the subjects were given oral fluconazole 400 mg and intravenous saline; oral placebo and intravenous fluconazole 400 mg; and oral placebo and IV saline. An oral dose of 7.5 mg of midazolam was ingested after fluconazole/placebo. The AUC and C_{max} of midazolam were significantly higher after oral than IV administration of fluconazole. Oral fluconazole increased the midazolam AUC and C_{max} by 272% and 129%, respectively. IV fluconazole increased the midazolam AUC and C_{max} by 244% and 79%, respectively. Both oral and IV fluconazole increased the pharmacodynamic effects of midazolam. (See **PRECAUTIONS**.)

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 800 mg oral dose of fluconazole on the pharmacokinetics of a single 1200 mg oral dose of azithromycin as well as the effects of azithromycin on the pharmacokinetics of fluconazole. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

Voriconazole: Voriconazole is a substrate for both CYP2C9 and CYP3A4 isoenzymes. Concurrent administration of oral Voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on Day 1, then 200 mg Q24h for 4 days) to 6 healthy male subjects resulted in an increase in C_{max} and AUCτ of voriconazole by an average of 57% (90% CI: 20% to 107%) and 79% (90% CI: 40% to 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. ~~Concomitant administration of voriconazole and fluconazole at any dose is not recommended. Close monitoring for adverse events related to voriconazole is recommended if voriconazole is used sequentially after fluconazole, especially within 24 h of the last dose of fluconazole.~~ (See **PRECAUTIONS**.)

Tofacitinib: Coadministration of fluconazole (400 mg on Day 1 and 200 mg once daily for 6 days [Days 2-7]) and tofacitinib (30 mg single dose on Day 5) in healthy subjects resulted in increased mean tofacitinib AUC and C_{max} values of approximately 79% (90% CI: 64% to 96%) and 27% (90% CI: 12% to 44%), respectively, compared to administration of tofacitinib alone. (See **PRECAUTIONS**.)

Abrocitinib: When coadministered with fluconazole (inhibitor of CYP2C9, 2C19, and 3A4), the systemic exposure (AUC) of abrocitinib was approximately 4.8-fold higher and the combined exposure (AUC) of abrocitinib and its active metabolites was approximately 2.5-fold higher compared to when abrocitinib was administered alone (See **PRECAUTIONS**).

Microbiology

Mechanism of Action

Fluconazole is a highly selective inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-α-demethylase. This enzyme functions to convert lanosterol to ergosterol. The subsequent loss of normal sterols correlates with the accumulation of 14-α-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole. Mammalian cell demethylation is much less sensitive to fluconazole inhibition.

Resistance

A potential for development of resistance to fluconazole is well known. Fungal isolates exhibiting reduced susceptibility to other azoles may also show reduced susceptibility to fluconazole. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known.

Fluconazole resistance may arise from a modification in the quality or quantity of the target enzyme (lanosterol 14-α-demethylase), reduced access to the drug target, or some combination of these mechanisms.

Point mutations in the gene (*ERG11*) encoding for the target enzyme lead to an altered target with decreased affinity for azoles. Overexpression of *ERG11* results in the production of high concentrations of the target enzyme, creating the need for higher intracellular drug concentrations to inhibit all of the enzyme molecules in the cell.

The second major mechanism of drug resistance involves active efflux of fluconazole out of the cell through the activation of two types of multidrug efflux transporters; the major facilitators (encoded by *MDR* genes) and those of the ATP-binding cassette superfamily (encoded by *CDR* genes). Upregulation of the *MDR* gene leads to fluconazole resistance, whereas, upregulation of *CDR* genes may lead to resistance to multiple azoles.

Resistance in *Candida glabrata* usually includes upregulation of *CDR* genes resulting in resistance to multiple azoles. For an isolate where the minimum inhibitory concentration (MIC) is categorized as Intermediate (16 to 32 mcg/mL), the highest fluconazole dose is recommended.

Candida krusei should be considered to be resistant to fluconazole. Resistance in *C. krusei* appears to be mediated by reduced sensitivity of the target enzyme to inhibition by the agent.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans*, which are often inherently not susceptible to TRIFLUCAN® I.V. (e.g., *Candida krusei*). Such cases may require alternative antifungal therapy.

Antimicrobial Activity

Fluconazole has been shown to be active against most isolates of the following microorganisms **both *in vitro* and in clinical infections.**

Candida albicans
Candida glabrata (Many isolates are intermediately susceptible)

Candida parapsilosis
Candida tropicalis
Cryptococcus neoformans

The following *in vitro* data are available, **but their clinical significance is unknown.** At least 90% of the following fungi exhibit an *in vitro* MIC less than or equal to the susceptible breakpoint for fluconazole (https://www.fda.gov/STIC) against isolates of similar genus or organism group. However, the effectiveness of fluconazole in treating clinical infections due to these fungi has not been established in adequate and well-controlled clinical trials.

Candida dubliniensis
Candida guilliermondii
Candida kefyr
Candida lusitaniae

Candida krusei should be considered to be resistant to fluconazole. Resistance in *C. krusei* appears to be mediated by reduced sensitivity of the target enzyme to inhibition by the agent.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans,* which are often inherently not susceptible to TRIFLUCAN® I.V. (e.g., *Candida krusei*). Such cases may require alternative antifungal therapy.

CLINICAL STUDIES

Cryptococcal meningitis: In a multicenter study comparing TRIFLUCAN® I.V. (200 mg/day) to amphotericin B (0.3 mg/kg/day) for treatment of cryptococcal meningitis in patients with AIDS, a multivariate analysis revealed three pretreatment factors that predicted death during the course of therapy: abnormal mental status, cerebrospinal fluid cryptococcal antigen titer greater than 1:1024, and cerebrospinal fluid white blood cell count of less than 20 cells/mm^3. Mortality among high risk patients was 33% and 40% for amphotericin B and TRIFLUCAN® I.V. patients, respectively (p=0.58), with overall deaths 14% (9 of 63 subjects) and 18% (24 of 131 subjects) for the 2 arms of the study (p=0.48). Optimal doses and regimens for patients with acute cryptococcal meningitis and at high risk for treatment failure remain to be determined. (Saag, *et al*. N Engl J Med 1992; 326:83-9.)

Pediatric Studies

Oropharyngeal candidiasis: An open-label, comparative study of the efficacy and safety of TRIFLUCAN® I.V. (2 to 3 mg/kg/day) and oral nystatin (400,000 I.U. 4 times daily) in immunocompromised children with oropharyngeal candidiasis was conducted. Clinical and mycological response rates were higher in the children treated with fluconazole.

Clinical cure at the end of treatment was reported for 86% of fluconazole-treated patients compared to 46% of nystatin treated patients. Mycologically, 76% of fluconazole treated patients had the infecting organism eradicated compared to 11% for nystatin treated patients.

	Fluconazole	Nystatin
Enrolled	96	90
Clinical Cure	76/88 (86%)	36/78 (46%)
Mycological eradication*	55/72 (76%)	6/54 (11%)

* Subjects without follow-up cultures for any reason were considered nonevaluable for mycological response.

The proportion of patients with clinical relapse 2 weeks after the end of treatment was 14% for subjects receiving TRIFLUCAN® I.V. and 16% for subjects receiving nystatin. At 4 weeks after the end of treatment, the percentages of patients with clinical relapse were 22% for TRIFLUCAN® I.V. and 23% for nystatin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Once opened, the product should be used immediately. Any unused infusion should be discarded.

From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° C to 8° C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30˚C. Do not freeze.

6.5 Nature and contents of container

Clear Type I glass infusion vial sealed closed with rubber stoppers and aluminium caps.

Pack sizes:
1 vial containing 50 ml, 100 ml or 200 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Fluconazole intravenous infusion is compatible with the following administration fluids:
a) Dextrose 5% and 20%
b) Ringer's solution
c) Hartmann's solution
d) Potassium chloride in dextrose
e) Sodium bicarbonate 4.2% and 5%
f) Aminosyn 3.5%
g) Sodium chloride 9 mg/ml (0.9%)
h) Dialaflex (interperitoneal dialysis Soln 6.36%)

Fluconazole may be infused through an existing line with one of the above-listed fluids. Although no specific incompatibilities have been noted, mixing with any other medicinal products prior to infusion is not recommended.

The solution for infusion is for single use only.
The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Hertzliya Pituach 46725

8. LICENSE NUMBER

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