**FLUCONAZOLE INJECTION**

**DESCRIPTION**

Fluclozonazole injection is an iso-osmotic, sterile, nonpyrogenic solution of fluconazole in a sodium chloride diluent. Each mL contains fluconazole 5 mg/mL in water for injection. The pH is approximately 5.0. Each mL contains 0.9 mg of sodium chloride. The solution is colorless or nearly colorless.

**INDICATIONS AND USAGE**

Fluclozonazole is indicated for the treatment of the following infections caused by susceptible microorganisms:

- As an alternative to amphotericin B for the treatment of invasive candidiasis, including candidemia, in patients who are intolerant to or in whom amphotericin B is not an option.
- For the treatment of esophageal candidiasis in patients who are intolerant to or in whom amphotericin B is not an option.

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**

Fluclozonazole is rapidly absorbed after oral administration and reaches peak plasma concentrations within 1 to 3 hours. The mean bioavailability of a single 150 mg injection is 79%. The plasma half-life is approximately 25 hours. The clearances of fluconazole in patients with normal renal function are 1.6 (± 0.6) L/hour. The volume of distribution at steady state is approximately 0.2 L/kg. The total serum clearance is 0.2 (± 0.1) L/hour. The clearance of fluconazole is reduced in patients with renal impairment, and the half-life is increased.

**Drug Interactions**

Fluclozonazole is a substrate for P-gp and CYP3A4 and can interact with drugs that are also substrates of these enzymes. These interactions can result in changes in the pharmacokinetics and/or pharmacodynamics of the drugs involved. Examples of such drugs include warfarin, cyclosporine, tacrolimus, midazolam, and amphotericin B.

**CONTRAINDICATIONS**

Fluclozonazole is contraindicated in patients with severe hepatic impairment, as the effects of the drug have not been established in such patients.

**PRECAUTIONS**

Life-threatening adverse reactions, including seizures, have been reported with the use of fluconazole in combination with other drugs, such as amphotericin B, in patients with HIV infection and cryptococcal meningitis. Therefore, the use of fluconazole in combination with other drugs should be avoided if possible.

**ADVERSE REACTIONS**

The most common adverse reactions associated with fluconazole use are headache, dizziness, and gastrointestinal symptoms, such as nausea and vomiting. Other adverse reactions include rash, pruritus, and fever. In severe cases, fluconazole may cause agranulocytosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

**PREGNANCY**

Fluclozonazole is a pregnancy category B agent. It is not known if fluconazole can cause fetal harm when administered to pregnant women. If fluconazole is administered to a pregnant woman, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus.

**NURSING MOTHERS**

It is not known whether fluconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fluconazole is administered to a nursing mother.

**Pediatric Use**

The safety and effectiveness of fluconazole in children have not been established. Therefore, fluconazole should not be used in children.

**Geriatric Use**

Fluclozonazole is not recommended for use in the elderly due to the risk of adverse reactions, including seizures.

**DRUG INTERACTIONS**

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were coadministered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

In a pharmacokinetic interaction study, coadministration of multiple dose hydrochlorothiazide to healthy volunteers increased the AUC of fluconazole by 98% and 24%, respectively, when fluconazole was administered orally and intravenously. Coadministration of hydrochlorothiazide with fluconazole increases the exposure to fluconazole in patients with renal impairment. (See Drug Interaction Studies)

Methadone: The ECG QTc interval has been reported to be prolonged in some patients receiving fluconazole. The effects of fluconazole on hepatic CYP3A4 isoenzymes may be of clinical significance and necessitate dose adjustment of methadone. Patients receiving methadone and fluconazole should be closely monitored. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

- Flucytosine: Fluconazole increases the AUC of flucytosine by approximately 90%, Cmax by approximately 120%, and decreases the plasma clearance of flucytosine by approximately 40%. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)
- Troleandomycin: Fluconazole decreased the maximum plasma concentration and area under the curve of troleandomycin. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)
- Kefamycin: Fluconazole decreased the maximum plasma concentration of kefamycin by approximately 40%. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)
- Azithromycin: Fluconazole decreased the area under the curve of azithromycin by approximately 50%. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

In general trials, fluconazole was coadministered with rifampin. Because of the occurrence of serious cardiac dysrhythmia necessary to predispose to the inability of fluconazole to penetrate cerebrospinal fluid (CSF), fluconazole was not coadministered with rifampin in critically ill patients with meningitis. However, fluconazole has been administered to patients with meningitis in combination with rifampin in clinical trials of acute meningitis and candida meningitis. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies and PRECAUTIONS: CNS Adverse Reactions)

Although there are no data on the pharmacokinetics of fluconazole in patients who are treated concomitantly with rifampin, the concurrent administration of both rifampin and fluconazole (ranging from 100 mg to 400 mg/day) resulted in approximately a 35 to 65% decrease in the mean AUC of fluconazole. This decrease is thought to be due to induction of hepatic monooxygenase activity which results in enhanced metabolism of fluconazole. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Propoxyphene: Plasma concentrations of propoxyphene and norpropoxyphene were increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Celecoxib: In studies of healthy volunteers, the AUC and Cmax of celecoxib were increased by 28% and 36%, respectively. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Amphotericin B: The AUC of amphotericin B was increased by 60% when administered with fluconazole. In rats, no teratogenic effects were found at fluconazole doses of up to 250 mg/kg. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Cyproheptadine: Cyproheptadine plasma concentrations were increased by up to 89.5%. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Methadone: In a pharmacokinetic interaction study of fluconazole with methadone, fluconazole resulted in substantial increases in methadone concentrations. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Phenytoin: No clinically significant interaction between phenytoin and fluconazole has been observed. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Clomipramine: The mean AUC of clomipramine was increased by 63% following coadministration of fluconazole. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Valproic Acid: The mean AUC of valproic acid was increased by 37% following coadministration of fluconazole. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

There have been reported interactions with warfarin, particularly in patients with recent gastrointestinal surgery or infection, who are at risk for an increased risk for bleeding. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

Protein Binding: Fluconazole is more than 97% bound to plasma proteins with no binding differences with concomitant medications or in patients with renal insufficiency. (See CLINICAL PHARMACOLOGY: Drug Interaction Studies)

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