Fluconazole

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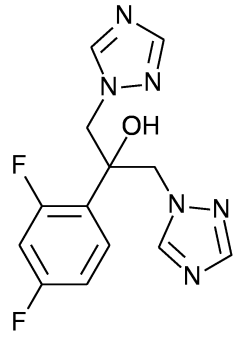
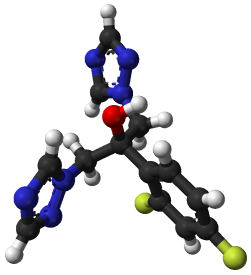




Systematic (IUPAC) name	
2-(2,4-difluorophenyl)-1,3-*bis*(1*H*-1,2,4-triazol-1-yl)propan-2-ol	
Identifiers	
CAS number	86386-73-4 [1]
ATC code	D01 AC15 [2] J02 AC01 [3]
PubChem	CID 3365 [4]
DrugBank	APRD00327 [5]
ChemSpider	3248 [6] ✓
UNII	8VZV102JFY [7] ✓
Chemical data	
Formula	$C_{13}H_{12}F_2N_6O$
Mol. mass	306.271 g/mol
SMILES	eMolecules [8] & PubChem [9]
Pharmacokinetic data	
Bioavailability	>90%
Protein binding	11–12%
Metabolism	Hepatic 11%
Half-life	30 hours (range 20-50 hours)
Excretion	Renal 61–88%

Therapeutic considerations	
Pregnancy cat.	D (Au), C (U.S.)
Legal status	S3/S4 (Au), POM (UK), ℞-only (U.S.)
Routes	Oral, IV, topical
✓ **(what is this?) (verify)** [10]	

Fluconazole (pronounced /fluːˈkɒnəzoʊl/) is a triazole antifungal drug used in the treatment and prevention of superficial and systemic fungal infections. In a bulk powder form, it appears as a white crystalline powder, and it is very slightly soluble in water and soluble in alcohol.[11] It is commonly marketed under the trade name **Diflucan** or **Trican** (Pfizer). In Mexico it is sold over the counter as **Alfumet**. It is marketed under the brand name "candivast" in the Persian Gulf area.

Pharmacology

Mode of action

Like other imidazole- and triazole-class antifungals, fluconazole inhibits the fungal cytochrome P450 enzyme 14α-demethylase. Mammalian demethylase activity is much less sensitive to fluconazole than fungal demethylase. This inhibition prevents the conversion of lanosterol to ergosterol, an essential component of the fungal cytoplasmic membrane, and subsequent accumulation of 14α-methyl sterols.[12] Fluconazole is primarily fungistatic, however may be fungicidal against certain organisms in a dose-dependent manner. It is interesting to note that, when fluconazole was in development at Pfizer, it was decided early in the process to avoid producing any chiral centers in the drug so that subsequent synthesis and purification would not encounter difficulties with enantiomer separation and associated variations in biological effect. A number of related compounds were found to be extremely potent teratogens, and were subsequently discarded.

Microbiology

Fluconazole is active against the following microorganisms:[13]

- *Blastomyces dermatitidis*
- *Candida* spp. (except *C. krusei* and *C. glabrata*)
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Epidermophyton* spp.
- *Histoplasma capsulatum*
- *Microsporum* spp.
- *Trichophyton* spp.

Pharmacokinetics

Following oral dosing, fluconazole is almost completely absorbed within two hours. Bioavailability is not significantly affected by the absence of stomach acid. Concentrations measured in the urine, tears, and skin are approximately 10 times the plasma concentration, whereas saliva, sputum, and vaginal fluid concentrations are approximately equal to the plasma concentration, following a standard dose range of between 100 mg and 400 mg per day. The elimination half-life of fluconazole follows zero order kinetics, and only 10% of elimination is due to metabolism, the remainder is excreted in urine and sweat. Patients with impaired renal function will be at risk of overdose as well as patients taking drugs such as warfarin.

Clinical use

Indications

Fluconazole is a prescription drug indicated for the treatment and prophylaxis of fungal infections where other antifungals have failed or are not tolerated (e.g., due to adverse effects), including:[14]

- Candidiasis caused by susceptible strains of *Candida*
- Tinea corporis, tinea cruris or tinea pedis
- Onychomycosis
- Cryptococcal meningitis

Fluconazole can be used first-line for the following indications:[14]

- Coccidioidomycosis
- Cryptococcosis
- Histoplasmosis
- Prophylaxis of candidiasis in immunocompromised people

Dosage

Dosage varies with indication and between patient groups, ranging from: a two-week course of 150 mg/day for vulvovaginal candidiasis, to 150–300 mg once weekly for resistant skin infections or some prophylactic indications. A dosage of 500–600 mg/day may be used for systemic or severe infections, and, in urgent infections such as meningitis caused by yeast, 800 mg/day have been used. Pediatric doses are measured at 6–12 mg/kg/d. A loading dose will be indicated when entering a daily dosage schedule; for example, a loading dose of 200 mg on the first day is commonly used with 150 mg/day following that.[14]

Contraindications

Fluconazole is contraindicated in patients that:[14]

- Have known hypersensitivity to other azole medicine
- Are taking Terfenadine, if 400 mg per day multidose of Fluconazole is administered
- Are in concomitant use of cisapride, due to risk of serious cardiac arrhythmias (relative contraindication)
- Are pregnant.

Precautions

Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of fluconazole in nursing mothers is not recommended.[15]

Fluconazole therapy has been associated with QT interval prolongation, which may lead to serious cardiac arrhythmias. Thus, it is used with caution in patients with risk factors for prolonged QT interval such as electrolyte imbalance or use of other drugs that may prolong the QT interval (particularly cisapride).

Fluconazole has also rarely been associated with severe or lethal hepatotoxicity and liver function tests are usually performed regularly during prolonged fluconazole therapy. In addition, it is used with caution in patients with pre-existing liver disease.[12]

High concentrations of fluconazole have been detected in human breast milk from patients receiving fluconazole therapy, thus its use is not recommended in breastfeeding mothers.[12]

Some people are allergic to azole(s). People allergic to other azole drugs might be allergic to fluconazole.[16] That is, some azole drugs have adverse side-effects. Some azole drugs may disrupt estrogen production in pregnancy, affecting pregnancy outcome.[17]

Fluconazole/Diflucan is in the FDA pregnancy category C.

This means that it is not known whether it will be harmful to an unborn baby. Do not take Fluconazole/Diflucan without first talking to your doctor if you are pregnant or could become pregnant during treatment.

Do not take Fluconazole/Diflucan if you are taking cisapride (Propulsid).

Combined with cisapride (Propulsid), Diflucan could cause serious, even fatal, heart problems.

In rare cases, Fluconazole/Diflucan has caused severe liver damage, sometimes resulting in death.

Notify your doctor immediately if you develop nausea, vomiting, abdominal pain, unusual fatigue, loss of appetite, yellow skin or eyes, itching, dark urine, or clay-colored stools.

These symptoms may be early signs of liver damage.

Severe allergic reaction like anaphylaxis has been reported (as listed in the data sheet of pfizer Diflucan). In rare cases, Fluconazole/Diflucan has also caused anaphylaxis, sometimes resulting in death. Notify your doctor immediately if you develop a rash while taking Fluconazole/Diflucan.[18]

Adverse effects

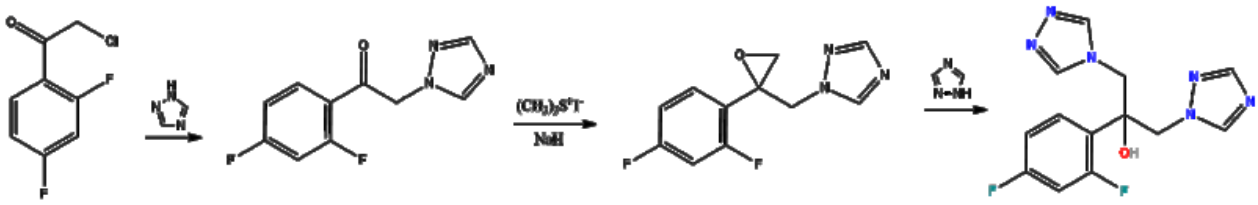
Adverse drug reactions associated with fluconazole therapy include:[14]

- Common (≥1% of patients): rash, headache, dizziness, nausea, vomiting, abdominal pain, diarrhea, and/or elevated liver enzymes
- Infrequent (0.1–1% of patients): anorexia, fatigue, constipation
- Rare (<0.1% of patients): oliguria, hypokalaemia, paraesthesia, seizures, alopecia, Stevens-Johnson syndrome, thrombocytopenia, other blood dyscrasias, serious hepatotoxicity including hepatic failure, anaphylactic/anaphylactoid reactions
- Very rare: prolonged QT interval, torsades de pointes

Drug interactions

Fluconazole is an inhibitor of the human cytochrome P450 system, particularly the isozymes CYP2C9 and CYP3A4. In theory, therefore, fluconazole decreases the metabolism and increases the concentration of any drug metabolised by these enzymes. In addition, its potential effect on QT interval increases the risk of cardiac arrhythmia if used concurrently with other drugs that prolong the QT interval. Berberine has been shown to exert synergistic effects with fluconazole even in drug-resistant *Candida albicans* infections.[19]

Synthesis



Richardson, R. K.; 1983, U.S. Patent 4,404,216 [20].

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