

FLUCONAZOLE

Trade: Diflucan

Can/Aus/UK: Diflucan

Uses: Antifungal, particularly candida infections

LRC: L2

AAP: Maternal Medication Usually Compatible with Breastfeeding

Fluconazole is a synthetic triazole antifungal agent and is frequently used for vaginal, oropharyngeal, and esophageal candidiasis. Many of the triazole antifungals (itraconazole, terconazole) have similar mechanisms of action and are considered fungistatic in action. In vivo studies have found fluconazole to have fungistatic activity against a variety of fungal strains including *C. albicans*, *C. tropicalis*, *T. glabrata*, and *C. neoformans*. The pharmacokinetics are similar following both oral and IV administration. The drug is almost completely absorbed orally (>90%). Peak plasma levels occur in 1-2 hours after oral administration. Unlike ketoconazole and itraconazole, fluconazole absorption is unaffected by gastric pH and does not require an acid pH to be absorbed. Steady state plasma levels are only attained after 5-10 days of therapy but can be achieved on day two with a loading dose (twice the daily dose) on the first day. Average plasma levels are 4.12 to 8.1 $\mu\text{g/mL}$. Fluconazole is widely and evenly distributed in most tissues and fluids and is distributed in total body water. Concentrations in skin and urine may be 10 fold higher than plasma levels. CSF concentrations are 50-94% of the plasma levels. Plasma protein binding is minimal at about 11%. Fluconazole is primarily excreted renally. Oral fluconazole is currently cleared for pediatric candidiasis for infants 6 months and older, and has an FDA Safety Profile for neonates 1 day and older. Clinical cure rate for oropharyngeal candidiasis in pediatric patients is reported at 86% with fluconazole (2-3 mg/kg/day) compared to 46% of nystatin treated patients. Fluconazole is transferred into human milk with a milk/plasma ratio of approximately 0.85.[1] Following a single 150 mg dose, milk levels at 2, 5, 24 and 48 hours were reported to be 2.93, 2.66, 1.76, and 0.98 $\mu\text{g/mL}$ respectively. Plasma levels at 2, 5, 24, and 48 hours were 6.4, 2.79, 2.52, and 1.19 $\mu\text{g/mL}$ respectively.[1] Other Plasma Kinetics: Plasma Half-Life= 35 hours Breastmilk Half-life= 30 hours From these data, and assuming an average milk level of 2.3 mg/L, an infant consuming 150 mL/kg/d of milk would receive an average of 0.34 mg/kg/d of fluconazole or 16% of the weight-adjusted maternal dose, and less than 5.8% of the pediatric dose (6 mg/kg/d). In another study of one patient receiving 200 mg daily (1.5 times the above dose) for 18 days, the peak milk concentration was 4.1 mg/L at 2 hours following the dose.[2] However, the mean concentration of fluconazole in milk was not reported. Pediatric Indications: While fluconazole is not cleared by the FDA for neonates, it is commonly used. It is however, cleared for infants 6 months and older. Due to the emergence of resistance to other antifungals, particularly nystatin, the use of fluconazole in pediatrics is increasing. Numerous reports now suggest that fluconazole is an effective and safe antifungal in low birth weight infants and neonates.[3,4,5,6,10] In one study of 40 low birth weight infants receiving fluconazole for up to 48 days, fluconazole produced few side effects.[7] Elevated liver enzymes were reported in only 2 of 40 serious ill LBW infants and due to other drugs; it is not known if this was associated with fluconazole therapy. Dosage Recommendations: Adult Vaginal Candidiasis: 150 mg PO-single dose. Oropharyngeal Candidiasis: Varies, but 200 mg STAT followed by 100 mg daily for up to 14 days is recommended. Systemic Candidiasis: For persistent or chronic infections, fluconazole has been used prophylactically in immunocompromised patients at a dose of 150 mg weekly to prevent recurrence[8,9]. Pediatric Dosing: The recommended pediatric dosing for oral candidiasis is 6 mg/kg STAT followed by 3 mg/kg/day. For systemic candidiasis, 6-12 mg/kg/day is generally recommended.[10] These current recommendations are for infants 6 months and older. The manufacturer states that a number of infants 1 day old and older have been safely treated. One study of premature infants suggests that the dose in very low birth weight infants should be 6 mg/kg every 2 to 3 days.[11] Availability: 50, 100, 200 mg tablets. Oral suspensions= 10 mg/mL and 40 mg/mL

Pregnancy Risk Category: C

Lactation Risk Category: L2

Adult Concerns: Adverse effects have only been reported in about 5-30% of patients, and in these, only 1-2.8% of patients have required discontinuation of the medication. Although adverse hepatic effects have been reported, they are very rare, and many occur coincident with the administration of other

medications in AIDS patients. The most common complications include vomiting, diarrhea, abdominal pain, and skin rashes.

Pediatric Concerns: Pediatric complications from oral ingestion include GI symptoms such as vomiting, nausea, diarrhea, abdominal pain. Nephrotoxicity has not been reported. No complications from exposure to breastmilk have found.

Drug Interactions: Decreased hepatic clearance of fluconazole results from use with cyclosporin, zidovudine, rifabutin, theophylline, oral hypoglycemics (glipizide and tolbutamide), warfarin, phenytoin, and terfenadine. Decreased plasma levels of fluconazole have resulted following administration with rifampin, and cimetidine.

Theoretic Infant Dose: 0.34 mg/Kg/Day

Relative Infant Dose: 16.1%

Adult Dose: 50-200 mg daily.

Alternatives:

T_{1/2} = 30 hours	M/P = 0.46-0.85
PHL = 88.6 hours (neonate)	PB = 15% .
T_{max} = 1-2 hours	Oral = >90%
MW = 306	pKa =
Vd =	

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