FLUCONAZOLE

(floo-*kon*-a-zole) Diflucan®

ANTIFUNGAL

Prescriber Highlights

- Oral or parenteral antifungal particularly useful for CNS infections
- Caution: Renal failure (dosage adjustment needed), pregnancy (safety not established), hepatic failure
- Adverse Effects: Occasional GI effects (inappetence) in cats or dogs; in humans: headache &, rarely, increased liver enzymes & hepatic toxicity
- Expensive, but price is decreasing now that it is available as a generic
- Drug Interactions

Uses/Indications

Fluconazole may have use in veterinary medicine in the treatment of systemic mycoses, including cryptococcal meningitis, blastomycosis, and histoplasmosis. It may also be useful for superficial candidiasis or dermatophytosis. Because of the drug's unique pharmacokinetic qualities, it is probably more useful in treating CNS infections or fungal urinary tract infections than other azole derivatives. Fluconazole does not have appreciable effects (unlike ketoconazole) on hormone synthesis and may have fewer side effects than ketoconazole in small animals.

Pharmacology/Actions

Fluconazole is a fungistatic triazole compound. Triazole-derivative agents, like the imidazoles (clotrimazole, ketoconazole, etc.), presumably act by altering the cellular membranes of susceptible fungi, thereby increasing membrane permeability and allowing leakage of cellular contents and impaired uptake of purine and pyrimidine precursors. Fluconazole has efficacy against a variety of pathogenic fungi including yeasts and dermatophytes. *In vivo* studies using laboratory models have shown that fluconazole has fungistatic activity against some strains of Candida, Cryptococcus, Histoplasma, and Blastomyces. *In vivo* studies of efficacy against Aspergillus strains have been conflicting.

Pharmacokinetics

Fluconazole is rapidly and nearly completely absorbed (90%) after oral administration. Gastric pH or the presence of food, do not appreciably alter fluconazole's oral bioavailability. It has low protein binding and is widely distributed throughout the body and penetrates well into the CSF, eye, and peritoneal fluid. Fluconazole is eliminated primarily via the kidneys and achieves high concentrations in the urine. In humans, fluconazole's serum half-life is about 30 hours in patients with normal renal function. Because of it's long half-life, fluconazole does not reach steady state plasma levels for 6–14 days after beginning therapy, unless loading doses are given. Patients with impaired renal function may have half-lives extended significantly and dosage adjustment may be required.

Contraindications/Precautions/Warnings

Fluconazole should not be used in patients hypersensitive to it or other azole antifungal agents. In patients with hepatic impairment it should be used only when the potential benefits outweigh the risks. Because fluconazole is eliminated primarily by the kidneys, fluconazole doses or dosing intervals may need to be adjusted in patients with renal impairment.

Fluconazole is reportedly toxic to budgerigars.

Adverse Effects

There is limited experience with this drug in domestic animals. Thus far, it appears to be safe to use in dogs and cats. Occasionally, inappetence may be reported.

In humans, the side effects have been generally limited to occasional GI effects (vomiting, diarrhea, anorexia/nausea) and headache. Rarely, increased liver enzymes and hepatic toxicity, exfoliative skin disorders, and thrombocytopenia have been reported in humans. Thrombocytopenia has not been reported thus far in animals.

Reproductive/Nursing Safety

Safety during pregnancy has not been established and it is not recommended for use in pregnant animals unless the benefits outweigh the risks. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Fluconazole is excreted in milk at concentrations similar to plasma. Use with caution in nursing dams.

Overdosage/Acute Toxicity

There is very limited information on the acute toxicity of fluconazole. Rats and mice survived doses of 1 g/kg, but died within several days after receiving 1–2 g/kg. Rats and mice receiving very high dosages demonstrated respiratory depression, salivation, lacrimation, urinary incontinence, and cyanosis. If a massive overdose occurs, consider gut emptying and give supportive therapy as required. Fluconazole may be removed by hemodialysis or peritoneal dialysis.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving fluconazole and may be of significance in veterinary patients:

- **AMPHOTERICIN B:** Lab animal studies have shown that fluconazole used concomitantly with amphotericin B may be antagonistic against Aspergillus or Candida; the clinical importance of these findings is not yet clear
- **BUSPIRONE:** Plasma concentrations may be elevated
- **CISAPRIDE:** Fluconazole may increase cisapride levels and the possibility for toxicity
- **CORTICOSTEROIDS:** Fluconazole may inhibit the metabolism of corticosteroid; potential for increased adverse effects
- **CYCLOPHOSPHAMIDE:** Fluconazole may inhibit the metabolism of cyclophosphamide and its metabolites; potential for increased toxicity
- **CYCLOSPORINE:** Increased cyclosporine levels
- **DIURETICS, THIAZIDES:** Increased fluconazole concentrations
- **FENTANYL/ALFENTANIL:** Fluconazole may increase fentanyl levels
- **MIDAZOLAM:** Increased midazolam levels and effects
- **NSAIDs:** Fluconazole may increase plasma levels; increased risk for adverse effects
- **RIFAMPIN:** May decrease fluconazole efficacy; fluconazole may increase rifampin levels
- **THEOPHYLLINE/AMINOPHYLLINE:** Increased theophylline concentrations

- **TRICYCLIC ANTIDEPRESSANTS** (**clomipramine, amitriptyline,** etc.): Fluconazole may exacerbate the effects of tricyclic antidepressants
- **SULFONYLUREA ANTIDIABETIC AGENTS** (*e.g.,* **glipizide**, **glyburide**): Fluconazole may increase levels; hypoglycemia possible
- **VINCRISTINE/VINBLASTINE**: Fluconazole may inhibit vinca alkaloid metabolism
- **WARFARIN**: Fluconazole may cause increased prothrombin times in patients receiving warfarin or other coumarin anticoagulants

Doses

- **DOGS:**
  a) General dosing guidelines: Give twice calculated daily dose for the first day of treatment; give for 2–3 days if rapidly advancing or severe disseminated mycosis. Give IV solution over 1–2 hours.

  For cryptococcosis, candidiasis, systemic mycoses, nasal aspergillosis: 2.5–5 mg/kg PO or IV q12–24h for 56–84 days. Often treat neurologic ocular cryptococcosis for at least 12 weeks or 2 weeks after CSF exam shows resolution of inflammation and antigen test results on serum and CSF are negative.

  For fungal meningitis: 5–8 mg/kg PO or IV q12h OR 8–12 mg/kg PO or IV once daily (q24h) for 56–84 days;

  For urinary candidiasis: 5–10 mg/kg PO q24h for 21–42 days;

  For urinary *Candida glabrata* infection: 12 mg/kg PO once daily for 21–42 days. (Greene, Hartmannn et al. 2006)

  b) For cryptococcosis: 5 mg/kg PO once or twice daily. Treatment should continue for at least 2 months beyond resolution of clinical signs. (Taboada 2000)

  c) For blastomycosis: 5 mg/kg PO q12h for 60 days

  For cryptococcosis: 5–15 mg/kg PO q12–24h for 6–10 months (Lemarie 2003b)

  d) For treatment of *Malassezia* (may be safer than itraconazole or ketoconazole in dogs with hepatic disease): 5 mg/kg PO once daily. (Thomas 2005b)

  e) For systemic treatment of *Malassezia* dermatitis: 5–10 mg/kg PO once daily to once a week. (Ihrke 2006)

  f) For systemic treatment of *Malassezia* dermatitis: 2–5 mg/kg PO once daily (q24h). (Beale and Murphy 2006)

- **CATS:**
  a) General dosing guidelines: Give twice calculated daily dose for the first day of treatment; give for 2–3 days if rapidly advancing or severe disseminated mycosis. For cryptococcosis or other systemic infections, treatment should continue until antigen testing results of blood or CSF are negative, this is usually at least 2 months beyond clinical resolution (mean time of 8 months treatment).

  For nasal or dermal cryptococcosis: 5–10 mg/kg PO q12–24h, or 10 mg/kg PO q24h; for most infections, 50 mg/cat PO once daily achieves adequate therapeutic levels.

  For CNS, intraocular, or multisystemic cryptococcosis: 50–100 mg/cat PO or IV q12h. Often treat neurologic ocular cryptococcosis for at least 12 weeks or 2 weeks after CSF exam shows resolution of inflammation and antigen test results on serum and CSF are negative.

  For CNS, intraocular or multisystemic mycoses: 50 mg/cat PO once daily (q24h); (Greene, Hartmannn et al. 2006)

  b) For cryptococcosis: 50 mg PO twice daily. Treatment should continue for 1 month beyond resolution of clinical signs. (Legendre 1995)

  c) For cryptococcosis: 50 mg PO twice daily. Treatment should continue for at least 2 months beyond resolution of clinical signs. (Taboada 2000)

- **RABBITS/RODENTS/SMALL MAMMALS:**
  a) Rabbits: 25–43 mg/kg slow IV q12h (Ivey and Morrisey 2000)

- **BIRDS:**
  a) As an alternate treatment of aspergillosis: 5–10 mg/kg PO once daily for up to 6 weeks, with or after amphotericin B (Oglesbee and Bishop 1994)

Monitoring

- Clinical Efficacy
- With long-term therapy, occasional liver function tests are recommended

Client Information

- Cost of this drug may be an issue. Fluconazole therapy may be prolonged (several weeks to months) and an average dosage in a cat (50 mg twice a day) may be very expensive
- Compliance with treatment recommendations must be stressed.
- Have clients report any potential adverse effects.

Chemistry/Synonyms

A synthetic triazole antifungal agent, fluconazole occurs as a white crystalline powder. It is slightly soluble (8 mg/mL) in water.

Fluconazole may also be known as UK-49858; many trade names are available.

Storage/Stability/Compatibility

Fluconazole tablets should be stored at temperatures less than 30°C in tight containers. Fluconazole injection should be stored at temperatures from 5–30°C (5–25°C for the *Viaflex*® bags); avoid freezing. Do not add additives to the injection.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Fluconazole Tablets: 50 mg, 100 mg, 150 mg, & 200 mg; *Diflucan*® (Pfizer); generic; (Rx)

Fluconazole Powder for Oral Suspension: 10 mg/mL & 40 mg/mL (when reconstituted) in 35 mL; *Diflucan*® (Roerig); (Rx)

Fluconazole Injection: 2 mg/mL in 100 mL or 200 mL bottles or *Viaflex Plus* (available with sodium chloride or dextrose diluents); *Diflucan*® (Pfizer); generic; (Rx)

FLUCYTOSINE

(floo-sye-toe-seen) Ancobon®

ANTIFUNGAL

Prescriber Highlights

- Antifungal used in combination (to reduce resistance development)
- Contraindicated in patients hypersensitive to it
- Extreme Caution: Renal impairment, preexisting bone marrow depression, hematologic diseases, or receiving other bone marrow suppressant drugs
- Caution: Hepatic disease
- Adverse Effects: Most common: GI disturbances; Potentially: dose dependent bone marrow depression, cutaneous eruption & rash primarily seen on the scrotum & nasal planum (in dogs), oral ulceration, increased hepatic enzymes, CNS effects in cats
- Dogs may not tolerate therapy for more than 10–14 days
- Teratogenic in rats

Uses/Indications

Flucytosine is principally active against strains of Cryptococcus and Candida. When used alone, resistance can develop quite rapidly to flucytosine, particularly with Cryptococcus. Because it penetrates relatively well into the CNS, it has been used in combination for the treatment of CNS cryptococcosis. Some cases of subcutaneous and systemic chromoblastosis may also respond to flucytosine. The drug can have synergistic efficacy when used with amphotericin B. Clinically, it is used primarily with amphotericin B in the treatment of cryptococcosis.

Pharmacology/Actions

Flucytosine penetrates fungal cells where it is deaminated by cytosine deaminase to fluorouracil. Fluorouracil acts as an antimetabolite by competing with uracil, thereby interfering with pyrimidine metabolism and eventually RNA and protein synthesis. It is thought that flucytosine is converted to fluorodeoxyuredylic acid that inhibits thymidylate synthesis and ultimately DNA synthesis.

In human cells, cytosine deaminase is apparently not present or only has minimal activity. Rats apparently metabolize some of the drug to fluorouracil, which may explain the teratogenic effects seen in this species. It is unclear how much cytosine deaminase activity dog and cat cells possess.

Pharmacokinetics

Flucytosine is well absorbed after oral administration. The rate, but not extent, of absorption will be decreased if given with food.

Flucytosine is distributed widely throughout the body. CSF concentrations may be 60–100% of those found in the serum. In healthy humans, the volume of distribution is about 0.7 L/kg. Only about 2–4% of the drug is bound to plasma proteins. It is unknown if flucytosine is distributed into milk.

Absorbed flucytosine is excreted basically unchanged in the urine via glomerular filtration. In humans, the half-life is about 3–6 hours in patients with normal renal function, but may be significantly prolonged in patients with renal dysfunction.

Contraindications/Precautions/Warnings

Flucytosine is contraindicated in patients hypersensitive to it.

Flucytosine should be used with extreme caution in patients with renal impairment. Some clinicians recommend monitoring serum flucytosine levels in these patients and adjusting dosage (or dosing interval) to maintain serum levels at less than 100 micrograms/mL. One clinician (Macy, 1987) recommends dividing the flucytosine dose by the serum creatinine level if azotemia develops.

Use flucytosine with extreme caution in patients with preexisting bone marrow depression, hematologic diseases, or receiving other bone marrow suppressant drugs. Flucytosine should also be used cautiously (with enhanced monitoring) in patients with hepatic disease.

Adverse Effects

Most common adverse effects seen with flucytosine are GI disturbances (nausea, vomiting, diarrhea). Other potential adverse effects include a dose dependent bone marrow depression (anemia, leukopenia, thrombocytopenia), cutaneous eruption and rash primarily seen on the scrotum and nasal planum (occurring in dogs), oral ulceration and increased levels of hepatic enzymes. Dogs receiving flucytosine often develop a severe drug reaction within 10–14 days of treatment.

Reports of aberrant behavior and seizures in a cat without concurrent CNS infection have been noted after flucytosine use. There are anecdotal reports of toxic epidermal necrolysis occurring in cats treated with flucytosine.

Reproductive/Nursing Safety

Flucytosine has caused teratogenic effects in rats. It should be used in pregnant animals only when the benefits of therapy outweigh the risks. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

It is not known whether this drug is excreted in milk. Because there are potential serious adverse reactions in nursing offspring, consider using milk replacer.

Overdosage/Acute Toxicity

No specifics regarding flucytosine overdosage were located. It is suggested that a substantial overdose be handled with gut emptying, charcoal and cathartic administration unless contraindicated.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving flucytosine and may be of significance in veterinary patients:

- **AMPHOTERICIN B:** When used with amphotericin B, synergism against Cryptococcus and Candida has been demonstrated *in vitro*. However, if amphotericin B induces renal dysfunction, toxicity of flucytosine may be enhanced if it accumulates. Should clinically significant renal toxicity develop, flucytosine dosage may need to be adjusted.

Laboratory Considerations

- When determining **serum creatinine** using the ***Ektachem***® analyzer, false elevations in levels may be noted if patients are also taking flucytosine.