Flucytosine

Antibiotic Class:
Antifungal agent

Antimicrobial Spectrum:
Fungi: *Candida albicans, C. glabrata, C. lusitaniae, C. krusei* (less susceptible), *Cryptococcus neoformans, Cladosporium* spp., *Phialophora* spp., *Fonsecaea pedrosoi, Saccharomyces cerevisiae, sporotrichosis, Rhodotorula, Penicillium, Paecilomyces, Aspergillus* spp. (less susceptible)

Mechanism of Action:
Penetrates the fungal cell wall and is converted to 5-fluorouracil which competes with uracil, thus interfering with fungal RNA and protein synthesis.

Pharmacodynamics:
Time-dependent Killing is most predictive of outcome, although AUC:MIC has some effects.

Pharmacokinetics:
Absorption: 80 to 90% absorption following oral administration
Distribution: low protein binding (~ 4% at serum concentrations between 2 and 55 µg/mL); widely distributes in body water (volumes of distribution from 0.6 to 0.9 L/kg); penetrates into CNS, urine, peritoneal fluid, and respiratory system
Metabolism: minimal hepatic metabolism
Elimination: renal elimination (urine); up to 96% of the total dose may be eliminated as unchanged drug

Adverse Effects:
Hematologic: leucopenia, thrombocytopenia, bone marrow aplasia
Gastric: intestinal perforation, ulcerating enterocolitis
Hepatic: elevated liver enzymes, hepatitis, jaundice, azotemia
Dermatologic: photosensitivity reaction
CNS (rare): headache, drowsiness, confusion, hallucinations

Dosage:
Oral dose: recommended dose 100 mg/kg/day in divided doses
Oral dose for severe infections: up to 250 mg/kg/day
Cryptococcal meningitis: 100 mg/kg/day

Disease state based dosing:
Renal Failure: Table 1
Hepatic failures: No dosage adjustment required.

Contraindications/Warnings/Precautions:
Warnings: Use extreme caution in patients with renal impairment, bone marrow suppression, or in patients with AIDS; dosage modification required in patients with impaired renal function

Drug Interactions:
Non-CYP mediated:
Aluminum hydroxide/Magnesium hydroxide – delay absorption of flucytosine
Zidovudine, ganciclovir, trimethoprim-sulfamethoxazole – may potentiate hematological toxicity
Amphotericin B and foscarnet – may potentiate toxicities related to excessive flucytosine levels

Pregnancy:
Category C: Risk unknown. Human studies inadequate.

Monitoring Requirements:
Therapeutic drug monitoring:
Goal: Serum flucytosine concentrations between 25 µg/mL and 100 µg/mL. Repeat assays on weekly basis.

Brand names/Manufacturer:

- ALCOBON (ICN, NZ) (Pacific - NZ)
- ALCOBON (Roche – IRELAND, SOUTH AFRICA)
- ANCOBON (ICN - USA)
- ANCOTIL (Hoffmann-La Roche – CANADA, BRAZIL) (CSP – FRANCE) (ICN - ITALY, UK, GERMANY, NETHERLANDS, SWITZERLAND, AUSTRIA, DENMARK, IRELAND, MALAYSIA, AUSTRALIA, SINGAPORE) (MEDILINK – SWEDEN, NORWAY) (Valeant – HONG KONG)
- NOVO-TRIPHYL (NOVOPHARM (CANADA))