

Emtricitabine

Brand Name: Emtriva

Drug Description

Emtricitabine, also referred to as FTC, is a nucleoside reverse transcriptase inhibitor (NRTI). Emtricitabine is the (-) enantiomer of a thio analogue of cytidine; it differs from other cytidine analogues by a fluorine in the 5 position. [1]

HIV/AIDS-Related Uses

Emtricitabine was approved by the FDA on July 2, 2003, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults age 18 and older. Emtricitabine may be considered for treatment-experienced adults with HIV that is susceptible to emtricitabine as assessed by genotypic or phenotypic testing.[2] Safety and effectiveness in pediatric patients have not been established, but pediatric clinical trials are currently underway.[3] [4]

Pharmacology

Emtricitabine, a synthetic nucleoside analogue of cytosine, undergoes phosphorylation by cellular enzymes to emtricitabine 5'-triphosphate. The active phosphate drug inhibits viral DNA synthesis by competing with the natural substrate deoxycytidine 5'-triphosphate for incorporation into viral DNA and terminating the DNA chain at the point of incorporation.[5]

Emtricitabine is rapidly and extensively absorbed following oral administration, reaching peak plasma concentrations (C_{max}) at 1 to 2 hours post-dose. In one clinical trial, the mean absolute bioavailability of emtricitabine was 93% following multiple doses of the drug. The mean steady state C_{max} was 1.8 mcg/ml and the area under the plasma concentration-time curve (AUC) over a 24-hour dosing interval was 10.0 hr-mcg/ml. The mean steady state plasma trough concentration 24 hours after an oral dose was 0.09 mcg/ml.[6]

Emtricitabine is in FDA Pregnancy Category B. Animal studies reveal no increased incidences of fetal variations or malformations in mice and rabbits at 60- and 120-fold higher drug exposures, respectively, than the human exposure at the

recommended daily dose. However, there are no adequate well-controlled studies in pregnant women. Results of animal studies are not always predictive of human response and emtricitabine should be used during pregnancy only if clearly needed. An antiretroviral pregnancy registry is established to monitor fetal outcomes of drug-exposed pregnant women. Healthcare providers can register patients at <http://www.APRRegistry.com> or by calling 1-800-258-4263. It is not known whether emtricitabine is distributed into human milk. Mothers should avoid nursing while on emtricitabine.[7]

Emtricitabine is less than 4% bound to plasma proteins, and protein binding is independent of drug concentration over a range of 0.02 to 200 mcg/ml. In vitro studies indicate that emtricitabine does not inhibit CYP450 enzymes. Biotransformation occurs through glucuronidation and oxidation. Following administration of ¹⁴C-emtricitabine, 86% of the dose was recovered in urine and 14% in feces. Of the urine-recovered dose, 13% was recovered as metabolites, including 3'-sulfoxide diastereomers and 2'-O-glucuronide. The plasma half-life of emtricitabine is approximately 10 hours. Renal clearance of the drug exceeds estimated creatinine clearance, indicating elimination by both glomerular filtration and active tubular secretion. In patients with renal impairment, C_{max} and AUC were increased.[8] Emtricitabine is 30% removed by hemodialysis, but peritoneal dialysis removal capabilities are unknown.[9]

HIV isolates with reduced susceptibility to emtricitabine have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. Viral isolates from 37.5% of patients with virologic failure had reduced susceptibility to emtricitabine, attributed to M184V/I mutations in the HIV reverse transcriptase gene. Cross resistance has been noted among some nucleoside analogues.

Emtricitabine-resistant isolates were cross-resistant to lamivudine and zalcitabine but retained susceptibility to abacavir, didanosine, stavudine, tenofovir, and zidovudine, as well as to the non-nucleoside reverse transcriptase inhibitors

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Pharmacology (cont.)

delavirdine, efavirenz, and nevirapine. Viruses harboring mutations of decreased susceptibility to stavudine, zidovudine, or didanosine remained sensitive to emtricitabine. Isolates containing K65R mutations demonstrated decreased susceptibility to emtricitabine.[10]

Adverse Events/Toxicity

The most frequently reported adverse effects of emtricitabine are mild to moderate headache, nausea, diarrhea, and skin rash. Skin discoloration on palms and soles, of unknown mechanism, was reported with higher frequency in emtricitabine-treated patients than in controls.[11]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including emtricitabine. In some patients coinfecting with HIV and hepatitis, exacerbation of hepatitis B has been reported after discontinuing treatment with emtricitabine.[12]

Redistribution of body fat, peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy.[13]

Treatment-emergent grade 3 or 4 laboratory abnormalities have been reported in at least 1% of patients receiving emtricitabine. These abnormalities include increased triglycerides greater than 750 mg/dl and increased creatine kinase greater than four times the upper limit of normal.[14]

Drug and Food Interactions

Emtricitabine may be administered with or without food; AUC was unchanged and C_{max} decreased by 29% when the drug was administered with a 1,000-calorie, high-fat meal.[15]

Emtricitabine has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (TDF), indinavir, famciclovir, and stavudine. Results showed no interactions except for a small increase in plasma trough

concentrations of emtricitabine when administered concurrently with TDF.[16] Because renal elimination of emtricitabine is through glomerular filtration and active tubular secretion, there may be competition for elimination with other compounds that are also renally eliminated.[17]

Contraindications

Emtricitabine is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the drug product. Emtricitabine should be discontinued in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or severe hepatotoxicity.[18]

Clinical Trials

For information on clinical trials that involve Emtricitabine, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Emtricitabine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[19]

Dosage Form: Capsules containing 200 mg emtricitabine.[20]

The recommended dose of emtricitabine for adults 18 years of age and older is 200 mg once daily. The dosing interval of emtricitabine should be adjusted in patients with baseline creatinine clearance (CrCl) less than 50 ml/min as follows: 200 mg every 48 hours for CrCl 30 to 49 ml/min; 200 mg every 72 hours for CrCl 15 to 29 ml/min; and 200 mg every 96 hours for CrCl less than 15 ml/min. Patients on hemodialysis should also receive emtricitabine 200 mg every 96 hours after completion of dialysis, if on the same day.[21]

Storage: Store at 25 C (77 F); excursions permitted at 15 C to 30 C (59 F to 86 F).[22]

Chemistry

CAS Name: (2R-cis)-4-Amino-5-fluoro-1-

Emtricitabine



Chemistry (cont.)

CAS Number: 143491-57-0[24]

Molecular formula: C₈-H₁₀-F-N₃-O₃-S[25]

C38.86%, H4.08%, F7.68%, N17.00%, O19.41%, S12.97%[26]

Molecular weight: 247.25[27]

Melting point: 136 C to 140 C (276.8 F to 284 F) as solid white from ether and methanol.[28]

Physical Description: White to off-white powder.[29]

Solubility: Approximately 112 mg/ml in water at 25 C (77 F).[30]

Other Names

524W91[31]

BW524W91[32]

FTC[33]

Coviracil[34]

Emtricitabina[35]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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