

Capravirine

Drug Class: Non-nucleoside Reverse Transcriptase Inhibitors

Drug Description

Capravirine is an imidazole type nonnucleoside reverse transcriptase inhibitor (NNRTI). [1]

HIV/AIDS-Related Uses

Capravirine is an NNRTI that exhibits potent in vitro antiviral activity against HIV variants with the K103N mutation. Capravirine's in vitro resistance profile suggested that capravirine would reduce plasma HIV RNA levels in NNRTI-experienced patients.[2]

Preliminary data from a phase II trial showed that NNRTI-experienced patients treated with nelfinavir, two nucleoside reverse transcriptase inhibitors (NRTIs), and capravirine had a decrease in plasma HIV RNA from baseline. However, there was no significant difference between the placebo and capravirine groups. On July 1, 2005, capravirine's manufacturer issued a press release stating that development of the drug will be discontinued. This decision was made after two clinical trials showed that capravirine was no more effective than currently approved anti-HIV drugs.[3]

Clinical trials of capravirine were suspended at one point for safety checks following the discovery that the drug causes vasculitis (inflammation of the blood vessels) in dogs. Vasculitis may cause severe damage to tissues supplied by inflamed blood vessels because blood cannot adequately reach the tissues. The trials were resumed following a year-long FDA investigation.[4]

Pharmacology

Capravirine inhibits replication of HIV-1 by interfering with the activity of the viral RNA-dependent DNA polymerase, reverse transcriptase (RT).

Studies of the three-dimensional structure of RT-NNRTI complexes have shown that NNRTIs all bind in a pocket. RT mutations that confer resistance to NNRTIs affect the amino acids that surround this pocket. Most mutations replace a

larger amino acid with a smaller one, thereby decreasing RT-NNRTI contact and reducing affinity. Capravirine is larger than other NNRTIs and has three main-chain, hydrogen-bonding interactions. This may account for capravirine's greater relative resistance to RT mutations; two mutations are required to confer high-level resistance to capravirine.[5]

Phase I trial data suggest that capravirine is ten times more potent than current NNRTIs. In clinical trials, capravirine has displayed linear pharmacokinetics and a half-life of approximately 2 hours. Mean decreases in viral load ranged from nearly 20-fold for a 700 mg twice-daily dosing regimen to nearly 50-fold for a 2,100 mg twice-daily dosing regimen, compared to a mean decrease of about 45-fold in patients treated with a triple therapy control arm receiving nelfinavir, zidovudine, and lamivudine.[6]

In vitro studies using human liver microsomes demonstrate that CYP3A is the major isoform for capravirine's metabolism; drugs that share this pathway may alter capravirine's pharmacokinetics.[7] Specifically, capravirine is metabolized by the CYP3A4 isoenzyme. When capravirine and lopinavir are taken concurrently, capravirine has been shown to decrease exposure to lopinavir, while lopinavir increases capravirine's concentrations.[8]

Adverse Events/Toxicity

Loss or distortion of taste, nausea, vomiting, diarrhea, and headache are the most frequently reported side effects of capravirine.[9] [10] Adverse effects occur more frequently at the 2,100 mg dose than at the 1,400 mg dose.[11]

Drug and Food Interactions

Capravirine can be taken with food.[12]

Twice-daily capravirine in combination with nelfinavir is well tolerated and achieves target drug concentrations. Nelfinavir increases the concentration of capravirine by approximately twofold.[13]

Capravirine



Drug and Food Interactions (cont.)

When capravirine was administered with atorvastatin, with or without lopinavir/ritonavir, in a study of healthy volunteers, capravirine increased atorvastatin exposure. Capravirine alone with atorvastatin increased atorvastatin exposure 2.6-fold; capravirine and lopinavir/ritonavir (LPV/r) administered with atorvastatin increased atorvastatin exposure 8.7-fold to 21-fold, depending on the doses of capravirine and LPV/r administered. Capravirine and LPV/r are metabolized by the CYP3A4 isoenzyme, and data indicate LPV/r increases capravirine's concentrations fivefold while 700 mg capravirine reduces LPV concentrations by 40%. [14]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[15]

Dosage Form: In clinical trials, capravirine has been dosed at 400 mg [16] , 700 mg, 1,400 mg [17] [18] , and 2,100 mg BID and 700 mg and 1,400 mg TID.[19]

Safety and efficacy data suggest that 1,400 mg BID may be the optimal dose.[20]

Chemistry

CAS Name:
5-[(3,5-Dichlorophenyl)thio]-4-(1-methylethyl)-1-(4-pyridinylmethyl)-1H-imidazole-2-methanol carbamate ester[21]

CAS Number: 178979-85-6[22]

Molecular formula: C₂₀H₂₀Cl₂N₄O₂S[23]

C53.22% H4.47% Cl15.71% N12.41% O7.09% S7.10%[24]

Molecular weight: 451.38[25]

Melting point: 88 C[26]

Physical Description: Crystals from diethylether as hemidehydrate.[27]

Other Names

S-1153[28]

AG1549[29]

CPV[30]

Further Reading

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Capravirine



Further Reading (cont.)

Raber SR et al. Addition of saquinavir (SQV) to a regimen of capravirine (CPV) plus lopinavir/ritonavir (LPV/r) does not alter systemic exposure of the antiretrovirals in healthy volunteers. Fifteen Annual International AIDS Conference, abstract TuPeB4631, 2004.

Manufacturer Information

Capravirine
Pfizer Inc
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New York, NY 10017-5755
(800) 438-1985

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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Capravirine



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