Amdoxovir

Drug Description

Amdoxovir is a dioxolane guanosine nucleoside analogue. [1]

HIV/AIDS-Related Uses

Amdoxovir, also known as DAPD, is an investigational nucleoside reverse transcriptase inhibitor (NRTI). It is being studied in HIV infected patients who have experienced virologic failure on previous antiretroviral regimens. In clinical studies, amdoxovir is given in combination with other antiretroviral agents or with mycophenolate mofetil.[2] [3]

Amdoxovir was being developed under a licensing agreement between Emory University, the University of Georgia Research Foundation, and Gilead Sciences. On January 28, 2004, Gilead announced that it was ending its agreement with Emory and the University of Georgia but that it would meet its ongoing obligations with respect to existing clinical trials. Gilead will cooperate with the universities during the transition to a new licensing agreement.[4]

Non-HIV/AIDS-Related Uses

Amdoxovir has activity against hepatitis B virus (HBV).[5] In laboratory animals, amdoxovir showed stronger inhibitory effects against HBV when given in combination with other antiviral agents than when given as single-drug therapy.[6]

Pharmacology

Amdoxovir is a purine nucleoside analogue. It is deaminated in vivo by adenosine deaminase to form the metabolite (-)-beta-D-dioxolane guanine (DXG). Biochemical analysis of the 5'-triphosphates of DAPD and DXG demonstrated that DXG 5'-triphosphate is a potent inhibitor of HIV reverse transcriptase.[7] In vitro tests of DXG demonstrated anti-HIV-1 activity that was comparable with that of lamivudine and abacavir, less than that of zidovudine and emtricitabine, and greater than that of stavudine, didanosine, and adefovir.[8] In vitro, DXG had synergistic antiviral activity with zidovudine, lamivudine, and nevirapine.[9]

Amdoxovir is rapidly absorbed and converted to DXG following oral dosing, and amdoxovir/DXG concentrations increase in a dose-dependent manner. Peak plasma concentrations of both amdoxovir and DXG occur within 1 to 2 hours after dosing. Plasma DXG concentrations are higher than those of amdoxovir, with a mean area under the plasma concentration-time curve (AUC) ratio (DXG to amdoxovir) ranging from 4 to 12. Amdoxovir has a half-life of approximately 1 hour and is eliminated from plasma primarily by conversion to DXG. DXG has a plasma half-life of approximately 7 hours.[10]

Toxicology studies in animals have shown that amdoxovir and DXG are excreted by the kidneys. The limited aqueous solubility of amdoxovir and DXG results in precipitation as urine is concentrated. Patients with renal insufficiency may be at greater risk for obstructive nephropathy and should not receive amdoxovir until additional clinical testing is completed.[11] [12]

Amdoxovir differs structurally from currently approved NRTIs by the replacement of the 3' carbon of the carbohydrate moiety with an oxygen atom. In vitro analysis indicated that HIV-1 resistant to zidovudine, lamivudine, didanosine, zalcitabine, and abacavir was susceptible to DXG. Virus resistant to nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) was also susceptible to DXG, as was virus containing the multidrug resistance-associated mutations G333E and the SS insertion between codons 68 and 69. Virus containing a K65R and Q151M double mutation was fully resistant to DXG, whereas virus containing either mutation alone was moderately resistant.[13] [14] The L74V mutation also conferred DXG resistance.[15]

The K65R and L74V mutations conferred cross-resistance between DXG and other NRTIs in vitro. These data suggest that DXG should not be used in combination with 2',3'-dideoxynucleosides that select for the same resistance mutations. K65R

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Pharmacology (cont.)

and L74V mutations did not affect sensitivity to zidovudine. In fact, these mutations decreased zidovudine resistance when introduced into a zidovudine-resistant genetic background. The lack of cross-resistance to zidovudine and the decrease in zidovudine resistance by DXG-resistant mutations provide strong rationale for the use of zidovudine and amdoxovir in combination.[16]

A Phase I study of amdoxovir monotherapy in treatment-experienced and treatment-naive patients indicated that viral load reduction is more modest in treatment-experienced patients than in treatment-naive patients.[17]

Adverse Events/Toxicity

The major toxicity associated with amdoxovir in animal studies was obstructive nephropathy and was more frequent in small, water-conserving species such as mice, rats, and marmoset monkeys. In cynomolgus monkeys, which, like humans, produce less concentrated urine, there was no evidence of obstructive nephropathy at doses up to fivefold higher than the anticipated human dose. Obstructive nephropathy was reversible when detected early and dosing was stopped. Hyperglycemia was observed in some monkeys that had signs of renal toxicity, and early cataract formation was detected in several monkeys with hyperglycemia.[18]

In humans, amdoxovir is generally well tolerated. In clinical trials, the most frequently occurring adverse effects were headache, pain, nausea, diarrhea, skin rash, abdominal pain, malaise, and tooth disorder. Most of the adverse effects were mild and transient and not considered to be related to amdoxovir.[19] [20]

In one study, a patient with a history of kidney stones had an episode of renal colic and passed a kidney stone on Day 1. His creatinine levels were normal and he completed the study with no change in study medication and with no additional renal problems.

In another study, a patient experienced shortness of breath and chest tightness and discomfort, which resolved on study Day 16 after completing the 14-day dosing part of the study. In the same study, five patients withdrew after visually insignificant lens opacities were detected upon examination by an ophthalmologist.[21]

Drug and Food Interactions

Mycophenolic acid, the active metabolite of the immunosuppressant drug mycophenolate mofetil (MMF), enhances the anti-HIV activity of amdoxovir in vitro. Concurrent administration of amdoxovir and MMF and of amdoxovir, enfuvirtide, and tenofovir disoproxil fumarate in HIV-infected patients is being evaluated in clinical trials.[22] [23]

Mycophenolic acid and ribavirin were found to potentiate the anti-HBV activity of several guanine-based nucleoside analogues, including amdoxovir.[24]

Contraindications

Patients with renal insufficiency may be at great risk for obstructive nephropathy and should not be dosed with amdoxovir until additional clinical testing is completed.[25] Until adequate safety data is generated, amdoxovir should not be administered to pregnant women, nursing mothers, or women of childbearing potential not using effective methods of contraception.[26]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[27] [28]

Dosage Form: Capsules containing 150 mg or 250 mg of amdoxovir.[29] [30]

Storage: Store between 15 and 30 C (59 and 86 F).[31] [32]

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Chemistry

CAS Name: 1,3-Dioxolane-2-methanol, 4-(2,6-diamino-9H-purin-9-yl)-, (2R,4R)-[33]

CAS Number: 145514-04-1[34]

Molecular formula: C9-H12-N6-O3[35]

C 42.86%, H 4.79%, N 33.32%, O 19.03%[36]

Molecular weight: 252.23[37]

Other Names

DAPD[38]

(2R,4R)-4-(2,6-diamino-9H-purin-9-yl)-1,3-Dioxolane-2-methanol[39]

2,6 Diaminopurine dioxolane[40]

(2R-cis)-4-(2,6-Diamino-9H-purin-9-yl)-1,3-dioxolane-2-methanol[41]

DAPD cpd[42]

Further Reading

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Manufacturer Information

Amdoxovir
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333 Lakeside Dr
Foster City, CA 94404
(800) 445-3235

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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