

Apricitabine



Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Apricitabine, previously known as AVX754 and SPD754, is a nucleoside reverse transcriptase inhibitor (NRTI). Apricitabine is the negative enantiomer of a member of the 4-thio heterosubstituted nucleoside analogue class. It is a novel cytidine analogue with activity against HIV strains that are resistant to other NRTIs. [1] [2]

HIV/AIDS-Related Uses

Apricitabine is a deoxycytidine analogue entering Phase IIb studies for the treatment of HIV infection. It is being studied as a first choice, second regimen drug for the treatment of HIV infection in people who have failed treatment with lamivudine. Apricitabine received fast-track approval status from the FDA.[3] [4]

Pharmacology

Apricitabine selectively inhibits the HIV replication enzyme reverse transcriptase (RT) in the same manner as traditional NRTIs. Apricitabine is the negative enantiomer of a failed investigational racemic mixture NRTI and appears to retain pharmacodynamic activity with reduced toxicity. The drug does not convert to the positive enantiomer or racemic mixture in vivo.[5] [6] [7]

Apricitabine must be metabolized intracellularly to its triphosphate form, apricitabine-TP, to exhibit antiviral activity. Intracellular concentrations of the active triphosphate are proportional to plasma concentrations of apricitabine. Apricitabine-TP accumulates intracellularly with twice-daily dosing, has a half-life of 6 to 7 hours, and achieves maximum plasma concentrations (C_{max}) at approximately 4 hours post dose.[8] In Phase I studies, oral bioavailability of AVX754 was 65% to 80% with 1,600 mg to 400 mg single doses, respectively. Apricitabine is rapidly absorbed.[9] The time to C_{max} ranged from 1.5 to 1.7 hours and was unaffected by dose or gender. Plasma protein binding of apricitabine is less than 4%.[10] The drug appears to penetrate the cerebrospinal fluid. Apricitabine exhibits linear pharmacokinetics following administration of single and multiple

doses. Apricitabine is renally eliminated by glomerular filtration and active tubular secretion in the kidney.[11] [12] Elimination is unaffected by gender. Most of the parent drug is excreted within the first 8 hours.[13] [14] Apricitabine and its active triphosphate metabolite do not appear to inhibit or induce any of the major cytochrome P (CYP) 450 isozymes, including CYP1A2, 2A6, 2C9, 2D6, and 3A4.[15]

A pharmacokinetic study compared single and multiple doses of apricitabine 800 mg in 39 HIV uninfected and in 18 healthy participants. In addition, pharmacokinetics of the active triphosphate, apricitabine -TP, were compared in 9 HIV infected and 21 healthy participants who received apricitabine 600 mg twice daily for 8 or 4 days, respectively. Pharmacokinetics of apricitabine appear similar in HIV uninfected and healthy groups. After a single 800 mg dose, the maximum plasma concentration (C_{max}) was 7.9 mcg/ml in healthy participants and 7.2 mcg/ml in HIV infected participants. The area under the concentration-time curve (AUC) was similar between the groups as well at 44.9 mg h/l and 39.5 mg h/l, respectively. After 8 days of apricitabine 800 mg once daily administration, C_{max} was 8.4 mcg/ml and 9.7 mcg/ml in healthy and HIV infected groups, respectively; AUC was 41.8 mg h/l and 38.1 mg h/l, respectively. Apricitabine-TP C_{max} after 8 days in HIV infected participants was twofold higher than C_{max} observed after 4 days in healthy participants.[16]

In a 10-day study of apricitabine in antiretroviral-naïve, HIV infected adults, single apricitabine doses of 400, 800, 1,200, and 1,600 mg were evaluated. Viral load decreased significantly at 1 week across all doses: approximately 90% with 400 mg; nearly 95% with 800 mg; nearly 97% with 1,200 mg; and 95% with 1,600 mg. After 10 days of daily apricitabine treatment, viral load reductions of nearly 98% with 1,200 mg and 1,600 mg were significantly greater than the approximately 90% reduction seen with 400 mg. No CD4 count changes were observed.[17]

A Phase IIb dose-ranging trial in treatment-experienced HIV infected patients is

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Pharmacology (cont.)

ongoing to determine apricitabine activity in patients with HIV strains resistant to lamivudine and that have the M184V mutation. Responses to doses will be compared to each other and to lamivudine for 21 days and 24 weeks.[18]

Resistance to apricitabine develops slowly compared with other NRTIs such as lamivudine and is associated with the K65R, V75I, and M184V mutations. Apricitabine is active against zidovudine- and lamivudine-resistant viruses.[19] The presence of five thymidine analogue mutations (TAMs) resulted in a less than twofold median change in apricitabine activity. No new resistance-conferring mutations emerged after 10 days of monotherapy; patients with baseline nucleoside analogue mutations showed promising decreases in viral load.[20]

Adverse Events/Toxicity

Unlike its racemic mixture predecessor BCH-10652, apricitabine showed little sign of mitochondrial toxicity in an early safety study in monkeys. After 52 weeks of 100 mg/kg/day treatment with apricitabine, mild but reversible hyperpigmentation, gastrointestinal effects, and minimal red blood cell count changes were observed. No bone marrow or mitochondrial abnormalities occurred in the liver, heart, or skeletal muscle.[21] [22] Apricitabine is not mutagenic.[23] No evidence of mitochondrial toxicity has been observed in vitro at concentrations 30 times greater than C_{max}. [24]

In a 10-day, dose-ranging study of apricitabine monotherapy in 63 antiretroviral-naïve, HIV infected patients, apricitabine was well tolerated at all doses. No serious adverse events were reported, and no treatment required discontinuation. Headache was the most commonly reported adverse event in patients taking apricitabine (42% of study participants), but headache frequency was similar to that of the placebo group. Nasal congestion appeared slightly more common with apricitabine than with placebo. Myalgia was reported by 10% of patients receiving apricitabine, but the relationship between myalgia and apricitabine is unclear. Low-level lipase changes similar to those in the

placebo group and six cases of increased serum lipase that appeared unrelated to apricitabine were reported. Otherwise, no clinically significant laboratory changes were reported.[25] [26]

Drug and Food Interactions

Apricitabine bioavailability appears unaffected by food.[27]

Apricitabine displayed additive to synergistic antiviral activity in vitro against wild-type HIV-1 when combined with a range of antiretrovirals.[28] Specifically, apricitabine and lamivudine had additive antiviral activity by sharing a common anabolic pathway. In a Phase I study that combined apricitabine and lamivudine, lamivudine reduced intracellular AVX754-TP concentrations in a dose-dependent manner by four- to sixfold relative to the apricitabine-TP concentration alone. Apricitabine had no effect on lamivudine or lamivudine-triphosphate concentrations.[29] [30]

The effect of trimethoprim on apricitabine excretion was studied in isolated perfused rat kidney because trimethoprim inhibits the excretion of lamivudine, which is structurally similar to apricitabine. Trimethoprim inhibited the excretion of apricitabine and its metabolite BCH-335. Because renal excretion of apricitabine and lamivudine are inhibited by trimethoprim to similar extents, exposure of apricitabine would also be expected to increase in the presence of therapeutic concentrations of trimethoprim.[31]

Because apricitabine does not induce or inhibit any of the major CYP450 isozymes, there is a low potential for interaction with drugs that undergo hepatic CYP metabolism.[32]

A Phase I study in 18 healthy participants compared apricitabine monotherapy versus apricitabine combined with tipranavir. Tipranavir significantly reduces the plasma levels of some NRTIs, such as zidovudine and abacavir. However, no reduction in apricitabine plasma levels occurred with concomitant tipranavir.[33]

Coadministration of lamivudine and apricitabine to HIV infected cells in vitro decreased the conversion of apricitabine to its triphosphate, but apricitabine

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Drug and Food Interactions (cont.)

did not affect lamivudine phosphorylation.[34]

Clinical Trials

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

Dosing Information

Mode of Delivery: Oral.[35]

Dosage Form: Apricitabine is manufactured in capsule form.[36] Apricitabine has been studied at doses of 200, 400, 600, and 800 mg twice daily and at doses of 800, 1,200, and 1,600 mg once daily.[37] [38] No apparent differences have been seen between daily and twice daily dosing schedules. The twice daily dosing schedule provides adequate and sustained intracellular accumulation and has been chosen as the primary schedule for continued study; once daily dosing may be determined in later trials.[39]

Chemistry

CAS Name: 2(1H)-Pyrimidinone,

Apricitabine



Chemistry (cont.)

CAS Number: 160707-69-7[41]

Molecular formula: C₈H₁₁N₃O₃S[42]

C45%, H5%, N20%, O22%, S8%[43]

Molecular weight: 215.0[44]

Other Names

SPD754[45]

ATC[46]

AVX754[47]

Further Reading

A Phase II, Randomised, Double-Blind, Dose-Ranging Study of AVX754 Versus Lamivudine in Treatment-Experienced HIV-1 Infected Patients With the M184V Mutation in Reverse Transcriptase. Available at:

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Further Reading (cont.)

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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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