

DPC 817

Brand Name: Reverset



Drug Description

DPC 817 is a cytidine nucleoside analogue. [1]

HIV/AIDS-Related Uses

DPC 817 is an investigational agent with activity against HIV-1. DPC 817 is being studied in HIV infected patients to determine the safety, tolerability, and pharmacokinetics of the drug in two dosage forms: an enteric coated tablet and a buffered oral solution.[2]

Pharmacology

Like other nucleoside reverse transcriptase inhibitors (NRTIs), DPC 817 must be phosphorylated to the active 5'-triphosphate form, DPC 817-TP. DPC 817-TP inhibits HIV reverse transcriptase (RT) by competing with the natural substrate, dC-TP. When incorporated into HIV viral DNA, DPC 817-TP causes DNA chain termination.

DPC 817 is selective for inhibition of HIV RT relative to mammalian cellular DNA polymerase beta and mitochondrial DNA polymerase gamma.[3]

Available pharmacokinetic data are from primate studies; rhesus monkeys were selected because nucleoside analogues generally behave similarly in rhesus monkeys and humans.

Absorption of DPC 817 was variable after oral administration to rhesus monkeys; the average oral bioavailability of DPC 817 was 41%. The average values for the distribution and elimination half-lives were 0.7 and 3.6 hours, respectively. The maximum concentration of drug in serum (C_{max}) ranged from 21.1 to 47.5 micromoles and the time to C_{max} (T_{max}) ranged from 1 to 4 hours with no inverse correlation between these two parameters. The highest C_{max} (47.5 micromoles) corresponded to a T_{max} of 3 hours, whereas the lowest C_{max} (21.1 micromoles) corresponded to a T_{max} of 1 hour.

DPC 817 is scarcely bound by plasma proteins; the free fraction in human serum is 96%. (1) (Schnazi p 1398) Absorption rates ranged from 0.50 to 0.86

hours (average 0.6 hours); mean absorption times (MATs) were between 2.7 and 3.4 hours (average 3.1 hours). Variations in the calculated MATs after oral administration suggest that differences in gastric emptying times may be partially responsible for the variance in the concentrations in plasma achieved in these animals after oral dosing. However, other gastrointestinal tract factors have not been ruled out.

After IV administration of DPC 817 to rhesus monkeys, DPC 817 could be detected in the cerebrospinal fluid (CSF) at 0.5 hours. The DPC 817 concentration in CSF did not decline noticeably for up to 3 hours after administration. Following oral administration, 2 hours were required before DPC 817 was detected in CSF samples. At 3 hours after oral administration, the DPC 817 concentration in CSF reached the same level as that observed 3 hours after IV administration. The apparent C_{max}s in CSF were 1.7 and 1.4 micromoles at 3 hours after both oral and IV administration.

The median effective concentrations (EC₅₀) of DPC 817 against HIV-1 in acutely infected human lymphocytes is 0.07 micromoles. After both oral and IV administration, DPC 817 plasma and CSF concentrations were above the EC₅₀ for HIV-1 for a prolonged period of time. High and sustained antiviral levels were attained.

After IV administration of 33.3 mg/kg to rhesus monkeys, 76% of the original dose of DPC 817 was recovered unchanged in the urine within 8 hours. At 8 hours post oral administration, 25% of unchanged DPC 817 was recovered in the urine. Average values for renal clearance and for total systemic clearance were 0.31 and 0.43 l/kg/hr respectively. The high fraction of drug recovered in the urine indicates that DPC 817 is eliminated mainly by renal excretion.[4]

Adverse Events/Toxicity

Mitochondrial toxicity has been proposed as a mechanism to explain the relatively high degree of toxicity of NRTIs. In vitro studies of DPC 817 have shown no effect on mitochondrial function.[5]

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Clinical Trials

For information on clinical trials that involve DPC 817, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: DPC 817 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[6]

Dosage Form: Enteric coated tablets containing 50 mg of DPC 817 and buffered oral solution.[7]

Chemistry

CAS Name: beta-D-2',3'-didehydro-2',3'-dideoxy-5-fluorocytidine[8]

Stability: DPC 817 is unstable in an acidic environment. Oral preparations must be buffered, administered with an antacid, or administered in a formulation, such as enteric coated tablets, that protects the drug from stomach acid.[9]

Other Names

RVT[10]

D-D4FC[11]

Further Reading

Ma L, Hurwitz SJ, Shi J, Mcatee JJ, Liotta DC, McClure HM, Schinazi RF. Pharmacokinetics of the antiviral agent beta-D-2',3'-didehydro-2',3'-dideoxy-5-fluorocytidine in rhesus monkeys. *Antimicrob Agents Chemother.* 1999 Feb;43(2):381-4.

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Schinazi RF, Mellors J, Bazmi H, Diamond S, Garber S, Gallagher K, Geleziunas R, Klabe R, Pierce M, Rayner M, Wu JT, Zhang H, Hammond J, Bacheler L, Manion DJ, Otto MJ, Stuyver L,

Trainor G, Liotta DC, Erickson-Viitanen S. DPC 817: a cytidine nucleoside analog with activity against zidovudine- and lamivudine-resistant viral variants. *Antimicrob Agents Chemother.* 2002 May;46(5):1394-401.

Shi J, McAtee JJ, Schlueter Wirtz S, Tharnish P, Juodawlkis A, Liotta DC, Schinazi RF. Synthesis and biological evaluation of 2',3'-didehydro-2',3'-dideoxy-5-fluorocytidine (D4FC) analogues: discovery of carbocyclic nucleoside triphosphates with potent inhibitory activity against HIV-1 reverse transcriptase. *J Med Chem.* 1999 Mar 11;42(5):859-67.

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

References

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2. Protocol ID: 318A - p 1.
3. Antimicrob Agents Chemother - 2002 May;46(5):1394-401. (PMID 11959574)
4. Antimicrob Agents Chemother - 1999 Feb;43(2):381-4. (PMID 9925539)
5. Antimicrob Agents Chemother - 2002 May;46(5):1394-401. (PMID 11959574)
6. Protocol ID: 318A - p 1.
7. Protocol ID: 318A - p 1.
8. Pharmasset, Inc - Early Clinical Data on Reverset from a Study in HIV-Infected Patients. Available at: <http://www.pharmasset.com>. Accessed 2/25/03.
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10. Pharmasset, Inc - Early Clinical Data on Reverset from a Study in HIV-Infected Patients. Available at: <http://www.pharmasset.com>. Accessed 2/25/03.
11. Pharmasset, Inc - Phase 1 Clinical Study for HIV is Underway - A Promising New Antiviral Agent Available at:<http://www.pharmasset.com>. Accessed 2/5/03.