KP- 1461

Drug Class: **Nucleoside Reverse Transcriptase Inhibitors**

Drug Description

KP-1461 is a potent, non--chain-terminating, mutagenic deoxyribonucleoside analogue. Designated a DNA covert nucleoside, the drug consists of a modified base that incorporates randomly into HIV and pairs with multiple bases. [1] [2] [3]

HIV/AIDS-Related Uses

KP-1461, also known as SN1461, is in Phase Ia and IIa trials for the treatment of HIV-1 infection in adults.[4] [5]

Pharmacology

KP-1461 is the oral prodrug of KP-1212. KP-1461 is also known as SN1212.[6] KP-1461 introduces continual mutations into HIV during viral replication by reverse transcriptase (RT). These mutations decrease virus viability and are eventually lethal. This mechanism, selective viral mutagenesis or lethal mutagenesis, is novel to the nucleoside analogue class.[7]

Unlike approved nucleoside RT inhibitors (NRTIs) that contain a modified sugar and unmodified base, KP-1461 has a modified base that allows multiple base pairing. Because KP-1461 pairs with multiple bases, it is able to target all viral proteins rather than a single protein.[8] [9]

KP-1461, after conversion to KP-1212, is metabolized to a triphosphate and incorporated into the HIV-1 genome by RT. The drug is similarly incorporated into human mitochondrial DNA polymerase.[10] The active substance KP-1212 has been shown to inhibit antiviral activity in tissues after just one pass; accumulation has been shown to eradicate the virus entirely.[11] HIV strains treated with KP-1212 also showed increased sensitivity to zidovudine.[12]

KP-1461 is being evaluated in an ongoing Phase Ib, randomized trial. In this trial, 40 HIV infected people who have failed prior antiretroviral therapy are receiving escalating doses of KP-1461 or placebo in four cohorts. KP-1461 also is entering a Phase IIa, open-label trial to evaluate its safety, efficacy, and tolerability as monotherapy in 32 treatment-experienced, HIV infected people.[13] [14]

In laboratory tests, multiple tissue passes failed to induce resistant HIV isolates after several attempts.[15] No cross resistance has been observed with HIV strains resistant to common nucleoside analogues such as zidovudine, lamivudine, stavudine, and abacavir.[16]

Adverse Events/Toxicity

No significant genotoxicity was observed in vitro in Chinese hamster ovary cells or in human B cells.[17] At doses up to 2 g/kg, no toxicity was observed in dogs; lactate levels did not increase, reflecting a lack of mitochondrial toxicity.[18] KP-1461 appears safe and well tolerated in humans in Phase I studies, and no dose-related toxicities were observed in a completed Phase I study.[19] [20]

Clinical Trials

For information on clinical trials that involve KP-1461, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: KP-1461 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[21]

Other Names

SN1461[22]

SN1212 [metabolized drug][23]

KP-1212 [metabolized drug][24]

KP-1212/1461[25]

Further Reading

Novel anti-HIV agent enters Phase IIa clinical trial. Expert Rev Anti Infect Ther. 2007 Aug;5(4):540-1.

Harris KS, Brabant W, Styrchak S, Gall A, Daifuku R. KP-1212/1461, a nucleoside designed for the treatment of HIV by viral mutagenesis. Antiviral Res. 2005 Jul;67(1):1-9. PMID: 15890415

Harris K, Brabant B, Li L, Styrchak S, Gall A, Daifuku R. SN1212/1461 a Novel Mutagenic Deoxyribonucleoside Analog with Activity Against HIV. San Francisco, Abstract 532, 2004.

ClinicalTrials.Gov - Safety and Efficacy Study of KP-1461 to Treat ART-Experienced HIV+ Patients. Available at:

Further Reading (cont.)

Manufacturer Information

KP-1461
Koronis Pharmaceuticals
12277 134th Court NE, Suite 110
Redmond, WA 98052
(425) 825-0240

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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