

UC- 781

Drug Class: Microbicides

Drug Description

UC-781 is a thiocarboxanilide non-nucleoside reverse transcriptase inhibitor (NNRTI). [1]

HIV/AIDS-Related Uses

UC-781 is an NNRTI currently being developed as a vaginal microbicide to prevent HIV transmission. UC-781 has been studied in animal models and has entered a Phase I clinical trial in humans. UC-781 is now in Phase II trials in the United States and in Thailand.[2] [3]

Pharmacology

In vitro studies have shown UC-781 to be a rapid, tight-binding inhibitor of HIV-1 reverse transcriptase.[4] It is effective against transmission of both free-floating HIV particles and cell-associated HIV. UC-781 has an intracellular antiviral protective effect and a half-life of 5.5 days.[5] [6]

In vitro exposure of human cervical tissue to UC-781 for 30 minutes has resulted in 95% reduction of subsequent HIV infection. Furthermore, greater concentrations of UC-781 pretreatment have resulted in total protection of the cervical tissue from both X4- and R5-tropic HIV-1 isolates as well as from cell-associated HIV-1 infection. Twenty-minute incubation with UC-781 has completely protected the cervical tissue up to 48 hours post-treatment without associated tissue toxicity.[7]

UC-781 administered to cellular and tissue explant models as a 0.1% carbopol gel formulation has demonstrated a potent, dose-dependent effect against R5- and X4-tropic HIV infections in T cells. In human cervical explant cultures, UC-781 was able to not only inhibit direct infection of mucosal tissue but also to prevent dissemination of virus by migratory cells. UC-781 retained significant activity against direct tissue infection and migratory cell infection. UC-781 demonstrated prolonged inhibitory effects able to prevent both localized and disseminated infections up to 6 days post-treatment. In addition, a 2-hour exposure to

UC-781 prevented infection of lymphoid tissue when challenged up to 2 days later. Although a greater dose of UC-781 was required to inhibit infections of lymphoid versus cervical explant, that dose, equivalent to a 1:3,000 dilution, was less than the full dose provided in a 0.1% formulation.[8]

The prolonged protective effect of UC-781, characterized as a memory effect that continues to protect drug-treated cells from HIV-1 replication, has been demonstrated for up to 12 days.[9]

UC-781 has been studied with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine in vitro. A 1:1 molar combination of zidovudine plus UC-781 showed high-level synergy in inhibiting replication of a zidovudine-resistant clinical isolate of HIV. When a 1:1 molar combination of zidovudine and UC-781 was compared to use of either drug alone, HIV resistance development was significantly slower.[10]

The microbicidal activity of UC-781 has been studied in vitro against strains of HIV-1 resistant to UC-781 (UCR), efavirenz (EFVR), and nevirapine (NVPR). UC-781 was 10- to 100-fold less effective against resistant strains than wild-type virus. The drug was more effective against NVPR strains than UCR strains, and was less effective against EFVR strains than UCR strains. Efficacy of UC-781 was dose-dependent; 25 mcM UC-781 provided essentially equivalent microbicidal activity against NNRTI-resistant and wild-type virus. UC-781 formulations under current development contain concentrations approximately 100-fold greater than the 25 mcM concentration necessary for efficacy.[11]

Drug and Food Interactions

UC-781 exhibits synergy with the NRTI zidovudine in vitro.[12] The combination of UC-781 and another candidate microbicide, cellulose acetate 1,2-benzenedicarboxylate, resulted in effective synergy for inhibition of HIV-1 in vitro and in peripheral blood mononuclear cells. Concomitant administration provided complementary mechanisms of action and protected ex vivo

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Drug and Food Interactions (cont.)

lymphoid tissues from HIV infection.[13]

Clinical Trials

For information on clinical trials that involve UC-781, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: UC-781 AND HIV Infections.

Dosing Information

Mode of Delivery: Intravaginal.[14] Rectal.[15]

Dosage Form: Topical gel in 0.1%, 0.25%, or 1.0% concentrations.[16] [17] UC-781 has been studied in once-daily dosages for up to 7 days and in twice-daily dosages for up to 14 days.[18] [19]

Chemistry

CAS Name: 3-Furancarbothioamide,

Chemistry (cont.)

CAS Number: 178870-32-1[21]

Molecular formula: C17-H18-Cl-N-O2-S[22]

C60.8%, H5.4%, Cl10.6%, N4.2%, O9.5%,
S9.5%[23]

Molecular weight: 335.5[24]

Other Names

UC781[25]

UC 781[26]

Further Reading

Liu S, Lu H, Neurath AR, Jiang S. Combination of candidate microbicides cellulose acetate 1,2-benzenedicarboxylate and UC-781 has synergistic and complementary effects against human immunodeficiency virus type 1 infection. *Antimicrob Agents Chemother.* 2005 May;49(5):1830-6.

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Sassi AB, Isaacs CE, Moncla BJ, Gupta P, Hillier SL, Rohan LC. Effects of physiological fluids on physical-chemical characteristics and activity of topical vaginal microbicide products. *J Pharm Sci.* 2007 Oct 5 [Epub ahead of print].

Van Herrewege Y, Michiels J, Van Roey J, Franssen K, Kestens L, Balzarini J, Lewi P, Vanham G, Janssen P. In vitro evaluation of nonnucleoside reverse transcriptase inhibitors UC-781 and TMC120-R147681 as human immunodeficiency virus microbicides. *Antimicrob Agents Chemother.*

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Further Reading (cont.)

2004 Jan;48(1):337-9.

ClinicalTrals.gov- Phase I Study of Safety and Persistence of UC-781 Vaginal Microbicide.
Available at:

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Further Reading (cont.)

Manufacturer Information

UC-781
Cellegy Pharmaceuticals, Inc
3490 Oyster Point Boulevard
Suite 200
South San Francisco, CA 94080
(650) 616-2200

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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