CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-183

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA # 21-183 REVIEWER: LALJI MISHRA, Ph.D.

Date Submitted: 01/31/2000 Date Received: 02/01/2000
Date Assigned: 02/11/2000 Date Completed: 10/23/00

Sponsor: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492
Product name(s):
Proprietary: Videx[R] EC
Non-proprietary: Didanosine
Chemical: 2', 3'-dideoxyinosine
Route of Administration/Dosage Form: Oral/Capsule
Indication: Treatment of HIV-1 infected adult patients [redacted]

SUPPORTING DOCUMENTS: IND [redacted], NDA # 20-154, NDA # 20-155, NDA # 20-156, IND [redacted] IND [redacted] DMF [redacted]

BACKGROUND:

Bristol-Myers Squibb Company has developed new encapsulated enteric-coated beadlet formulation of didanosine (ddI) named Videx[R] EC capsules and seeks marketing approval (NDA # 21-183) of Videx[R] EC capsules for the treatment human immunodeficiency virus (HIV-1) infection in adult patients. ddI is a synthetic nucleoside analogue reverse transcriptase inhibitor (NRTI) and is FDA approved for the treatment of HIV-1 infection. ddI has been demonstrated to exhibit anti-HIV-1 activity both in vitro and in vivo. The pertinent microbiology data for ddI have been previously reviewed and can be found in the microbiology review of the NDA approval package for ddI (NDA # 20-154). The microbiology label was recently revised and approved by the FDA. The current microbiology label is shown here.

MICROBIOLOGY

Mechanism of Action

Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3'-hydroxyl (OH) group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5'-triphosphate. Dideoxyadenosine 5'-triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5'-triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.

In Vitro HIV Susceptibility

The in vitro anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug necessary to inhibit viral replication by 50% (IC_{50}) ranged from 2.5 to 10 μM (1 μM = 0.24 μg/mL) in lymphoblastic cell lines and 0.01 to 0.1 μM in monocyte/macrophage cell cultures. The relationship between in vitro susceptibility of HIV to didanosine and the inhibition of HIV replication in humans has not been established.

Drug Resistance

HIV-1 isolates with reduced susceptibility to didanosine have been selected in vitro and were also obtained from patients treated with didanosine. Genetic analysis of isolates from didanosine-treated patients showed mutations in the reverse transcriptase gene that resulted in the amino acid substitutions K65R, L74V and M184V. The L74V mutation was most frequently observed in clinical isolates. Phenotypic analysis of HIV-1 isolates from 60 patients (some with prior zidovudine treatment) receiving 6 to 24 months of didansine monotherapy showed that isolates from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine in vitro compared to baseline isolates. Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutations. The clinical relevance of genotypic and phenotypic changes associated with didanosine therapy has not been established.

Cross-resistance

HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with zidovudine and didanosine exhibited decreased susceptibility to zidovudine, didanosine, zalcitabine, stavudine and lamivudine in vitro. These isolates harbored five mutations (A62V, V75I, F77L, F116Y and Q151M) in the reverse transcriptase gene. The clinical relevance of these observations has not been established.

RECOMMENDATIONS

With respect to microbiology, this NDA (21-183) is supported.

/S/ 10/23/00

Microbiologist

CONCRRENCES:

HFD-530/Dep Dir /S/, Signature 10/24/00 Date

HFD-530/MicroTL_____ Signature _____ Date

CC: /S/ 10/23/00

HFD-530/ Original NDA # 21-183

APPEARS THIS WAY
ON ORIGINAL

HFD-530/Division File
HFD-530/Micro TL
HFD-530/Review Micro
HFD-530/CSO, Sillivan, D.