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

NDA 20-154 REVIEWER: LALJI MISHRA, Ph.D.
(Desk copy)

Date Submitted: 04/30/99

Sponsor: Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

PRODUCT NAME(s):
Proprietary: Videx
Non-proprietary: Didanosine
Chemical: 2',3'-dideoxyinosine
Route of Administration/Dosage Form: Oral, Tablets
Indication: Treatment of HIV-1 infected adult patients and children over 6 months of age

BACKGROUND

Bristol-Myers Squibb has submitted revisions to the package insert for didanosine (ddI). The revised version of the 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 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 (dATP), 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 sensitivity 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 didanosine monotherapy therapy 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.

RECOMMENDATION:

The revised microbiology section of the ddI package insert described as above is acceptable.

(S)

Microbiologist

CONCURRENCES:

HFD-530/Dep Dir Signature _____ Date

HFD-530/Micro (S) Signature 9/9/99 Date

CC:

HFD-530/ Original NDA 20-154/20-155/20-156
HFD-530/Division File
HFD-530/Micro TL
HFD-530/Review Micro
HFD-530/CSO, Sillivan, D.