



NDA 20-154/S-050
NDA 20-155/S-039
NDA 20-156/S-040
NDA 21-183/S-016

CHANGES BEING EFFECTED

Bristol-Myers Squibb Pharmaceutical Company
Attention: Nancy Mason-Liddil
Associate Director, Global Regulatory Sciences
5 Research Parkway
Signature 91 Building, 3SIG-513
Wallingford, CT 06492

Dear Ms. Mason-Liddil:

Please refer to your supplemental new drug applications dated May 24, 2006 received on May 25, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products:

- Videx[®] (didanosine) Chewable/Dispersible Buffered Tablets 25 mg, 50 mg, 100 mg, 150mg, and 200 mg
- Videx[®] (didanosine) Buffered Powder for Oral Solution 45 mg, 67mg, 100 mg, 167 mg, 250 mg, and 375 mg
- Videx[®] (didanosine) Pediatric Powder for Oral Solution 2mg/bottle, and 4gm/bottle
- Videx[®] EC (didanosine) Delayed Release Capsules 125 mg, 200 mg, 250 mg, and 400 mg

We acknowledge receipt of your amendments dated September 6, 2006 and received on September 7, 2006.

These "Changes Being Effected" supplemental new drug applications provide the addition of text in the **MICROBIOLOGY** section of the package insert for Videx[®] and Videx EC[®] in response to a request from the FDA dated November 16, 2005. In addition, the following labeling changes are made:

- To incorporate changes deleting Videx[®] (didanosine) Chewable/Dispersible Buffered Tablets and relevant information
- To incorporate same text change in the **WARNINGS: Hepatic Impairment and Toxicity** section like supplement NDAs 20-154/SLR49, 20-155/SLR038, 20-156/SLR039, and 21-183/SLR015 approved on August 18, 2006

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In your next printing of the Videx[®] and Videx[®] EC labels, please revise the “*In Vitro* HIV Susceptibility”, “Resistance”, and “Cross-resistance” subsections in the **MICROBIOLOGY** section of the Videx[®] and Videx[®] EC labels to read as follows:

HIV Susceptibility in Cell Culture

The 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% (EC₅₀) 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.

Resistance

HIV-1 isolates with reduced sensitivity to didanosine have been selected in cell culture 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 showed that isolates from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine in cell culture 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 cell culture. These isolates harbored five mutations (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. In data from clinical studies, the presence of thymidine analogue mutations (M41L, D67N, L210W, T215Y, K219Q) has been shown to decrease the response to didanosine.

We completed our review of these supplemental new drug applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on May 24, 2006.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Monica Zeballos, Pharm.D., Regulatory Project Manager, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Approved labeling (package insert and patient package insert) for Videx[®] and Videx EC[®]

**This is a representation of an electronic record that was signed electronically and
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/s/

Debra Birnkrant
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NDA 21-183, 20-155, 20-156, 20-154