CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-655/S-032
19-910/S-021
20-518/S-004

MEDICAL REVIEW

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FROM DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation IV/Division of Antiviral Research Drug Products

DATE: March 16, 2001

TO: NDA 19,655/S-032; RETROVIR Capsules
NDA 19,910/S-021: RETROVIR Syrup
NDA 20,518/S-004; RETROVIR Tablets

FROM: Katherine Laessig, M.D.
Medical Officer, HFD-530

THROUGH: Jeffrey Murray, M.D., M.P.H.
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SUBJECT: NDA 19,655/S-032; NDA 19,910/S-021; NDA 20,518/S-004
Labeling Supplement

The sponsor has submitted a labeling supplement to update the RETROVIR label and make it consistent with the labels of COMBIVIR and EPIVIR. After review of the submission, a major change to the Description of Clinical Studies was recommended to describe more succinctly and update the clinical studies of RETROVIR. In addition, several other minor changes were recommended, as noted below. Otherwise, the changes to the label, described in detail in the CSO review of Dr. Holloman, were found to be acceptable. The following comments were faxed to the sponsor.

1. Under the **Clinical Pharmacology** section, lines 154 to 157 should be deleted and replaced with:

   Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

2. For **Table 4,** would the rifampin interaction data be suitable to add to this table? If so, please add this to table 4.

3. Under the **Description of Clinical Studies** section, Monotherapy in Adults subsection, replace lines 287-292 with the following:

Monotherapy in Adults: In controlled studies of treatment-naïve patients conducted between 1986 and 1989, [redacted], as compared to placebo, reduced the risk of HIV disease progression, as assessed using endpoints that included the occurrence of HIV-related illnesses, AIDS-defining events, or death. These studies enrolled patients with advanced disease (BW002), and asymptomatic or mildly symptomatic disease in patients with CD4 cell counts between 200 and 500 cells/mm^3 (ACTG016 and ACTG019). A survival benefit for RETROVIR monotherapy was not demonstrated in the latter two studies. Subsequent studies showed that the clinical benefit of RETROVIR monotherapy was time limited.

4. Under Precautions, immediately following the Drug Interactions subtitle, add the following statement. See Clinical Pharmacology section (Table 4) for information on zidovudine concentrations when coadministered with other drugs. For patients experiencing pronounced anemia or other severe zidovudine-associated events while receiving chronic coadministration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

5. Under **Precautions, Drug Interactions** (lines 454-460) delete the subtitle, [redacted] Create another subtitle, "Overlapping toxicities" for lines 457-458. Doxorubicin should also have its own subtitle, and should be placed after line 430.

   In addition, for line 455-6, please indicate for which drug the AUC was decreased. As it is currently written, this is unclear.

6. Under the **Adverse Events** section on lines 578 and 617, delete "Combination Therapy" and "Monotherapy," respectively. Since there are no adverse event tables referring to combination therapy specifically, the subtitle, "Adults" will suffice.

7. Under the **Dosage and Administration** section, at the end of line 795, add: For patients experiencing pronounced anemia while receiving chronic coadministration of zidovudine and some of the drugs (e.g., fluconazole, valproic acid) listed in Table 4, zidovudine dose reduction may be considered.

   Line 800, add a period at the end of the sentence.

cc: HFD-530/Division Files
HFD-530/CSO/Holloman
HFD-530/ActgDivDir/Birnkrant
HFD-530/MOTL/Murray
HFD-530/MO/Laessig

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/s/

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