CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-857/S-008

MEDICAL REVIEW

AUG 29 2000

NDA: 20-857 (SLR-008)

Medical Officer's Review
NDA Labeling Supplement

Date submitted:	August 26, 1999
Date received:	August 27, 1999
Date assigned:	September 13, 1999
Draft MOR completed:	February 15, 2000
Revisions to MOR completed:	August 15, 2000

Applicant: Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Drug name: Combivir™ (lamivudine/zidovudine tablets)

Dosage form: Tablets containing lamivudine 150 mg and zidovudine 300 mg

Route of administration: Oral

Proposed indication: Treatment of HIV infection

Related INDs and NDAs:

[redacted]

NDA 20-564 (lamivudine tablets 150 mg)
NDA 20-596 (lamivudine solution 10 mg/ml)
NDA 20-857 (lamivudine/zidovudine tablets)

Amendments:

August 31, 1999
April 3, 2000
August 10, 2000

Background

Combivir® is a fixed-dose combination of lamivudine and zidovudine which was approved in September 1997. It contains doses of the two component drugs corresponding to available approved dosage formulations of the separate drugs, which are antiretroviral nucleoside analogues. Zidovudine has been approved since 1987 for treatment of HIV infection when treatment is warranted, and lamivudine since 1995 (as Epivir®) for use in combination with zidovudine. A lower dose of lamivudine was approved in 1998 as Epivir-HBV for treatment of chronic hepatitis B. The current supplement is submitted in response to regulatory requirements for geriatric information in product package inserts.

Proposed changes in labeling, and FDA comments

The applicant has concluded that clinical studies have not included a large enough number of geriatric patients to evaluate similarities or differences compared to younger patients, and has proposed labeling to reflect this. Minor changes in wording were suggested in a comment to the sponsor, for closer correspondence to language models in 21 CFR 201.57(f)(10); these were also consistent with the consensus of a Division meeting to discuss geriatric labeling. The proposed label wording was also referred to Biopharmaceutics because information from a pharmacokinetic study of lamivudine in a small number of elderly Japanese subjects was included (and not considered adequate for label information).

The applicant agreed with the wording changes suggested for the geriatric section, and in their response to that issue made additional changes to the labeling including changes in the description of the product coating and a change in the wording of the box warning. The changes in description of the drug product were referred to Chemistry for review. The change in the box warning (which was not mentioned in the covering letter and was not flagged in the label revision) altered the approved sentence "ZIDOVUDINE, ONE OF THE TWO ACTIVE INGREDIENTS IN COMBIVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS)" to "ZIDOVUDINE [redacted] ACTIVE INGREDIENTS IN COMBIVIR, HAS BEEN ASSOCIATED WITH HEMATOLOGIC TOXICITY INCLUDING NEUTROPENIA AND SEVERE ANEMIA, PARTICULARLY IN PATIENTS WITH ADVANCED HIV DISEASE (SEE WARNINGS)." It has been evident in other recent label changes that the applicant has been using numerals for all numbers as house style (but has flagged such changes rather than introducing them without mention). However, as the word [redacted] is also conspicuous and potentially distracting in reading the box warning. The applicant was asked to restore the approved version of the box warning.

In an amendment dated August 10, 2000, the applicant restored the box warning wording, and flagged changes from [redacted] number of these changes involve portions of the labeling customarily reviewed by Pharmacology/Toxicology, and were therefore informally discussed with Pharmacology/Toxicology. As informal comments from Chemistry, Biopharmaceutics, and Pharmacology/Toxicology have indicated no objections, the geriatric wording now appears consistent with the CFR and with Division consensus on geriatric wording, and the box warning is consistent with the previously approved version, the labeling in this amendment appears suitable for approval.

/S/

Barbara Styrt, M.D., M.P.H.
Medical Officer, HFD-530

Concurrence:
HFD-530/Dir/HJolson HJ 8/29/00
HFD-530/MTL/SKukich 8/29/00

cc:
HFD-530/NDA20857
HFD-530/Division File
HFD-530/Pharm/Farrelly
HFD-530/Micro/Battula
HFD-530/Chem/Lo
HFD-530/Stat/Aras
HFD-530/Biopharm/Reynolds
HFD-340
HFD-530/MO/BStyrt
HFD-530/MTL/SKukich
HFD-530/CSO/Kelly

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