

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-857/S-008

ADMINISTRATIVE DOCUMENTS

Division of Antiviral Drug Products

SEP 13 2000

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-857/S-008

Name of Drug: Combivir™ (lamivudine/zidovudine) tablets

Sponsor: Glaxo Wellcome Inc.

Material Reviewed

Submission Dates: August 26, and 31, 1999, and April 3, and August 10, 2000.

Receipt Dates: August 27, and September 1, 1999, and April 4, and August 11, 2000

Background and Summary Description:

This supplemental application provides for a geriatric use section in the Combivir label. This package insert was compared electronically to the final printed labeling submitted February 16, 2000, approved January 21, 2000 (supplement 006).

Review

The revisions to the Combivir package insert were as follows:

1. On page 1, under **DESCRIPTION: COMBIVIR:**, second paragraph, the following paragraph had the underline section added and the strikethrough section deleted.

COMBIVIR Tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose. _____

_____ polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

2. Numbers throughout the package insert have been changes to digits

3. Under **CLINICAL PHARMACOLOGY**, page 6, The following sentence was deleted:

4. The following section was added under **PRECAUTIONS**, on page 12:

Geriatric Use: Clinical studies of COMBIVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. COMBIVIR is not recommended for patients with impaired renal function (i.e., creatinine clearance \leq 50 mL/min; see **PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION**).

Conclusions

All of the changes noted in the labeling review were acceptable. An approval letter will be sent to the sponsor and they will be asked to submit a final printed labeling identical to the draft labeling submitted August 10, 2000, for the package insert.

151
Regulatory Health Project Manager 13-SEPT-2000

cc:

Original 20-857

HFD-530/Div. Files 20-857

HFD-530/Kelly

CSO REVIEW



MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: March 8, 2000

To: Martha Anne Moore, R.Ph.

Address: GlaxoWellcome
Fax- 919-483-5756

From: Christine Kelly, RN, MS, MBA, Project Manager

Through: Stanka Kukich, M.D., Medical Team Leader
Barbara Styrt, M.D., Medical Reviewer 3/8/00

NDA: 20-857

Subject: Labeling supplement S-008 which provides for geriatric labeling changes

The following comments are being conveyed on behalf of Dr. Styrt regarding the proposed Geriatric labeling section for the COMBIVIR label (NDA 20-857, SLR-008). Additional comments may follow. Please also provide your rationale for deletion of the existing "Geriatric Patients" subsection in the Clinical Pharmacology section.

Clinical Comments

Geriatric use: Clinical studies of COMBIVIR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

COMBIVIR is not recommended for patients with impaired renal function (i.e., creatinine clearance ≤ 50 mL/min; see PRECAUTIONS: Patients with Impaired Renal Function and DOSAGE AND ADMINISTRATION).

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

(S)

Christine Kelly, MS, MBS, RN
Regulatory Health Project Manager

Page: 2
March 7, 2000

Division of Antiviral Drug Products

cc:
NDA/IND
Division File
HFD-530/TL/Kukich
HFD-530/MO/Styrt
HFD-725/PM/Kelly

Facsimile

GlaxoWellcome

ARCHIVAL COPY – 1 COPY OF LABELING

October 26, 2000

Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850



FA
SLR 008

**Re: NDA 20-857/S-008; COMBIVIR® Tablets (lamivudine/zidovudine tablets)
General Correspondence: Final Printed Labeling**

Not Br [initials]

Dear Dr. Jolson:

Please refer to our supplemental new drug application dated August 26, 1999 for Combivir (lamivudine/zidovudine) Tablets, which provides for a Geriatric Use subsection of PRECAUTIONS in the package insert. Please also refer to our amendments dated August 31, 1999; April 3, 2000; and August 10, 2000; and to your approval letter dated September 29, 2000.

We are submitting herewith 20 copies of a final printed package insert that is identical to the draft labeling submitted on August 10, 2000. We are also providing a desk copy containing a diskette in Word format directly to Ms. Christine Lincoln, Regulatory Health Project Manager, of your Division.

If you have any questions regarding this submission, please contact me at (919) 483-9347. Thank you.

Sincerely,

Martha Anne A. Moore

Martha Anne A. Moore, R.Ph.
Product Director
Antiviral/Anti-Infective Regulatory Affairs

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

ORIGINAL

GlaxoWellcome

August 10, 2000



Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850

NDA SUPPLEMENTAL AMENDMENT

BL

SLR-008

**Re: NDA 20-857; COMBIVIR® Tablets (lamivudine/zidovudine tablets)
Response to FDA Request/Comment: Labeling**

Dear Dr. Jolson:

Reference is made to our submission of August 26, 1999 which provided for a supplemental NDA (sNDA-008) for the proposed wording for the geriatric use section of our Combivir labeling. Reference is also made to the facsimile received from your Division on March 8, 2000 which provided comments on our submission of August 26, 1999, and to our amendment dated April 3, 2000. On May 15, 2000, we received comments regarding our April 3, 2000 submission via facsimile from your Division. The purpose of this submission is to provide our response to the comments provided by your Division on May 15, 2000 and to provide an updated label.

Clinical comments contained in the March 8, 2000 FDA facsimile have been incorporated into the Combivir label provided via this submission; these changes have been indicated with revision marks and are highlighted in yellow. We are also indicating changes previously made to the label that will be reported in the next Combivir NDA annual report; these changes have been marked with revision marks, are highlighted in blue, and bulleted below. Please note that these annual reportable changes are only minor editorial changes.

- We had changed the words _____ the boxed warning to be consistent with recent recommendations of the American Medical Society *Manual of Style* 9th Edition (Chapter 16.1). To comply with your May 15, 2000 request, we have reverted to the words "one of the two" in the black box. However, elsewhere throughout the insert, numbers have been changed to digits and are included with the revisions marked for S-008.

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

ORIGINAL

Heidi M. Jolson, M.D., M.P.H.

August 10, 2000

Page 2

- Under the DESCRIPTION section of the label, we have deleted the words _____ providing instead the full listing of the ingredients in the _____ formulation found in the film coating solution.

This submission is made in duplicate to NDA 20-857 along with a diskette containing WORD files for the labeling. In addition, four (4) desk copies along with one diskette have been provided directly to Ms. Christine Kelly for use by the review team. If you have any questions regarding this submission, please contact me at (919) 483-9347. Thank you.

Sincerely,

A handwritten signature in cursive script that reads "Martha Anne A. Moore".

Martha Anne A. Moore, R.Ph.

Product Director - Antiviral/Anti-Infective Regulatory Affairs

GlaxoWellcome

April 3, 2000

Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850

NDA SUPPL AMENDMENT



**Re: NDA 20-857; COMBIVIR® Tablets (lamivudine/zidovudine tablets)
Response to FDA Request/Comment
Amendment to Pending Application: Labeling Supplement S-008**

SLR-008 BL

*NM 8/17/00
BA*

Dear Dr. Jolson:

Reference is made to our submission of August 26, 1999 which provided for a supplemental NDA (sNDA-008) for proposed wording for the geriatric labeling of our Combivir NDA 20-857. Reference is also made to the facsimile received from your Division on March 8, 2000 which provided comments on our submission of August 26th. The purpose of this submission is to provide our response to the comments provided by your Division on March 8th and to provide an updated label based upon FDA comments.

Clinical comments contained in the March 8th FDA facsimile have been incorporated into the version of the Combivir label provided via this submission. We are providing a revision-marked and a clean copy of the currently approved product labeling (attachments 1 & 2). In addition to incorporating Division clinical comments, we have also updated the base copy of the insert as approved on January 21, 2000 in S-006, added patent information and described the ingredients in the formulation.

As requested, we would like to provide our rationale for deleting the Geriatric Patients subsection of the Clinical Pharmacology section. The report summary for Study LB-05 "Comparison of Pharmacokinetics of Lamivudine Between Elderly Volunteers and Healthy Young Male Volunteers" was included in the NDAs for Eпивir-HBV Tablets (NDA21-003, Volume 13, page 72) and Oral Solution (NDA 21-004). This summary report was also submitted in the August 26, 1999 submission to NDAs 20-564 and 20-596. This study, conducted in December 1996/January 1997, is the only formal analysis of the effects of age on lamivudine pharmacokinetics, and was carried out in Japanese subjects who were >65 years of age but otherwise healthy (n=6) compared with a group of young subjects (n=6). In these elderly patients, the age-related reduction in renal

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0-4-00/CC*

Heidi M. Jolson, M.D., M.P.H.

April 3, 2000

Page 2

clearance resulted in moderate (40%) but clinically insignificant increases in daily exposure of lamivudine. Other parameters were not significantly affected; therefore, in this small sample size, it can be concluded that dose modification is not required on the basis of age alone unless accompanied by significant renal dysfunction. With this information, we did not believe it was accurate to leave the current statement in the product labeling stating "pharmacokinetics have not specifically been studied in patients over 65 years of age," knowing there is data available on a small number of subjects. Please find a copy of the report under attachment 3.

In addition, there is not a Geriatric Patients subsection in the Clinical Pharmacology section of the Epivir-HBV product labeling, which was approved in December 1998. In an effort to be consistent, and because as stated above, the data available is very limited, the statement was not included in the recently revised Epivir or Combivir product labeling.

We look forward to any additional comments on the draft labeling. This information is being provided in duplicate to the NDA 20-857. Four desk copies and one diskette have been provided directly to Ms. Christine Kelly for use by the review team. Please contact me at (919) 483-9347 for any matters regarding this submission. Thank you.

Sincerely,

A handwritten signature in cursive script that reads "Martha Anne A. Moore". The signature is written in black ink and is positioned below the word "Sincerely,".

Martha Anne A. Moore, R.Ph.

Project Director - Antiviral/Anti-Infective Regulatory Affairs



Food and Drug Administration
Rockville MD 20857

NDA 20-857/S-008

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

SEP 7 1999

Attention: Martha Anne A. Moore, R.P.H.
Antiviral Group-Regulatory Affairs

Dear Ms. Moore:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Combivir® (lamivudine/zidovudine) Tabs

NDA Number: 20-857

Supplement Number: S-008

Date of Supplement: August 26, 1999

Date of Receipt: August 27, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 26, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely

Anthony W. DeCicco
Supervisory Consumer Safety Officer
Division of Anti-Viral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

NDA 20-857/S-008

Page 2

cc:

Original NDA 20-857/S-008

HFD-530/Div. Files

HFD-530/CSO/C. Kelly

SUPPLEMENT ACKNOWLEDGEMENT

GlaxoWellcome

ORIGINAL

August 26, 1999

Heidi M. Jolson, M.D., M.P.H., Director
Division of Antiviral Drug Products
Attn: Document Control Room
Food and Drug Administration
Fourth Floor, HFD-530
9201 Corporate Blvd.
Rockville, MD 20850

NDA NO. 20857 REF NO. 008
NDA SUPPL FOR SLR



Re: NDA 20-857; COMBIVIR® Tablets (lamivudine/zidovudine tablets)
Supplemental Application: Geriatric Labeling

Dear Dr. Jolson:

Reference is made to our New Drug Application 20-857 for Combivir Tablets. Also please reference the August 27, 1997 final rule on Specific Requirements on Content and Format of Labeling for Human Prescription Drugs: Addition of "Geriatric Use" Subsection in the Labeling and the December 1998 Guidance for Industry on Content and Format for Geriatric Labeling.

This supplement is being submitted in compliance with the above referenced regulation. The Geriatric use labeling for Combivir is being revised under 21 CFR 201.57(f)(10)(ii)(A). A User Fee is not applicable as there are no clinical data being submitted to support a labeling change.

Neither lamivudine, zidovudine nor the combination product, Combivir, has been specifically studied in a geriatric patient population. A review of patient enrollment for five large, multicenter, randomized clinical trials (NUCB3007, CNAAB3005, ACTG 320, AG 511 and DMP 006) indicates the typical patient enrolled in HIV clinical trials falls below 65 years of age. Results from these trials, as well as a literature review, support our proposed labeling that clinical studies did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger subjects. Our proposed labeling changes for Combivir are in agreement with the regulations.

As part of our submission, we are providing a revised package insert. In addition to the clean copy with accepted revisions, a package insert showing all changes from the currently approved package insert with revision bars in the right margin is also provided. Added text is underlined; deleted text is lined through. We are also enclosing a diskette containing the package insert as a Word file.

Glaxo Wellcome Inc.

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North Carolina 27709-3398

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919 483 2100

*Please see
review dated
9-13-99
@Lincoln/CS*

Heidi M. Jolson, M.D., M.P.H.

August 26, 1999

Page 2

This submission is provided in duplicate. Four additional desk copies are being provided directly to Ms. Christine Kelly for use by the review team. If you have any questions regarding this submission, please contact me at (919) 483-9347. Thank you.

Sincerely,

A handwritten signature in black ink that reads "Martha Anne A. Moore". The signature is written in a cursive style with a long, sweeping tail on the letter "e".

Martha Anne A. Moore, R.Ph.

Antiviral Group - Regulatory Affairs



NDA 20-857/S-008

GlaxoWellcome Inc.
Attention: Martha Anne A. Moore, R.Ph.
Antiviral Group-Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC
27709

Dear Ms. Moore:

We acknowledge the receipt of your October 26, 2000 submission containing final printed labeling in response to our September 29, 2000 letter approving your supplemental new drug application for Combivir™ (lamivudine/zidovudine), 150mg/300mg tablets.

We have reviewed the labeling that you submitted in accordance with our September 29, 2000 letter, and we find it acceptable.

If you have any questions, call Christine Lincoln, RN, MS, MBA, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

Debra Birnkrant, MD.
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

/s/

Debra Birnkrant

12/21/00 04:50:14 PM