CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-154

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-154

COMPLETE RESPONSE

Novartis Pharmaceuticals
Attention: Michael S. Buska, Director Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Buska:

Please refer to your new drug application (NDA) dated December 21, 2007, received December 21, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TYZEKA® (telbivudine) oral solution.

We have completed the review of your application, as amended and have determined that we cannot approve this application in its present form. Before the application may be approved, you must address the following:

1. For patients with End Stage Renal Disease, the proposed

b(4)

2.

b(4)

3.

b(4)

4. Please submit revised carton and/or container labels as follows:

- Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.**"

5. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

6. You must submit a proposed REMS, as described below.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

Since TYZEKA® (telbivudine) tablet formulation was approved in 2006, we have become aware of the development of peripheral neuropathy, in some cases resulting in motor weakness, pain, sensory deficits and/or difficulty walking in patients taking TYZEKA® (telbivudine). At this time, insufficient data are available to determine whether these symptoms are fully reversible after discontinuation of TYZEKA® (telbivudine). Residual neurologic deficits have been reported in patients when TYZEKA® (telbivudine) was continued after the development of neuropathy symptoms. This information is from the review of your supplemental new drug application adding long-term data for TYZEKA® (telbivudine) tablets, from the review of your new drug application (NDA 22-154) for TYZEKA® (telbivudine) oral solution, and from postmarketing adverse event reports. This information was not available when TYZEKA® (telbivudine) tablet formulation was granted marketing authorization. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for TYZEKA® (telbivudine) oral solution to ensure the benefits of the drug outweigh its risks. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must contain the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. We have determined the patient package insert you submitted on May 30, 2008, should be converted to a Medication Guide which must include the new safety information regarding the risk of peripheral neuropathy described above. Pursuant to 21 CFR Part 208, FDA has determined that TYZEKA®

(telbivudine) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of TYZEKA® (telbivudine). FDA has determined that TYZEKA® (telbivudine) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or to continue to use TYZEKA® (telbivudine). Under 21 CFR 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed TYZEKA® (telbivudine).

Timetable for Assessment: The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than by 18 months and 3 years, and in the 7th year after the REMS is initially approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the assessment interval.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of TYZEKA® (telbivudine)
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your NDA. Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-154 PROPOSED REMS

If your initial proposed REMS is revised, please send 5 copies of any subsequent submission related to the proposed REMS identified as follows:

NDA 22-154 PROPOSED REMS AMENDMENT

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what further steps need to be taken before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

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

Enclosure: REMS Template
REMS Supporting Document Template

Appendix A- REMS Template

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:
A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use
    c. Implementation System
    d. Timetable for Assessment of the REMS

4. Information Needed for Assessments

5. Other Relevant Information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
10/21/2008 04:52:39 PM
NDA 22-154