DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-154 **NDA APPROVAL**

Novartis Pharmaceuticals Corporation
Attention: Michael S. Buska
Director, Drug 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 for TYZEKA® (telbivudine) oral solution.

We acknowledge receipt of your submissions dated August 30, 2007 (presubmission), January 3, 2008, September 19, 2008, September 22, 2008, October 21, 2008, October 29, 2008, February 27, 2009, April 8, 2009, April 24, 2009 and April 27, 2009.

The February 27, 2009 submission constituted a complete response to our October 21, 2008 action letter.

This new drug application provides for the use of TYZEKA® (telbivudine) oral solution for the treatment of chronic hepatitis B (CHB) in adult patients with evidence of viral replication and active liver inflammation and CHB patients with renal impairment who may require a dose reduction.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

We acknowledge your April 27, 2009 submission containing final printed carton and container labels.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the Medication Guide). Upon receipt, we will transmit that version to

the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved NDA 22-154."**

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C.355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are deferring submission of your pediatric studies for ages birth to < 2 years until September 30, 2016, pending a final decision regarding risk/benefit of treatment in this age group. We are deferring submission of pediatric studies for ages 2 to 18 years until September 30, 2013, because this application is ready for approval in adults and the pediatric date are not yet available.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study/substudy for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from 2 to <18 years of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from 2 to < 18 years of age to support dose-selection for the efficacy and safety assessment.

   Protocol Submission: completed
   Study Start Date: March, 2009
   Final Report Submission: September, 2010

2. Deferred pediatric study for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from 2 through < 18 years of age. Using doses selected based on the substudy listed under item 1 above, conduct a pediatric safety and efficacy study of telbivudine with efficacy based on virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.

   Protocol Submission: March, 2010
   Study Start Date: September, 2010
   Final Report Submission: September, 2013

3. Deferred pediatric PK dose selection and efficacy studies in patients from birth to < 2 years of age. Studies in pediatric patients 2 to < 18 years age should be completed before determining whether it is appropriate to study telbivudine for HBV in the birth to < 2 years age group. According to experts in pediatric HBV disease (pediatric hepatologists), treatment is rarely initiated in the first two years of life in patients with chronic HBV infection and this group may be waived in the future if this continues to be the consensus at the time the safety data are available from older pediatric patients or if the risk/benefit assessment is not favorable based on that data.

Protocol Submission: January, 2013
Study Start Date: March, 2013
Final Report Submission: September, 2016

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated **"Required Pediatric Study Commitments."**

POSTMARKETING COMMITMENTS

We remind you of your postmarketing commitment in your submission dated April 24, 2009. This commitment is listed below:

4. Develop a dosing cup for distribution with Tyzeka oral solution that has clearly marked units of measure and contains only those units that correspond to dosing recommendations included in the prescribing information.

   sNDA Submission: January 2010

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risk (section 505-1(a)).

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. 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 continue to use, TYZEKA® (telbivudine). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed TYZEKA® (telbivudine).

As noted in our letter dated October 21, 2008, we have become aware that peripheral neuropathy, in some cases resulting in motor weakness, pain, sensory deficits and/or difficulty walking, has been reported in patients taking TYZEKA® (telbivudine) tablets alone or in combination with pegylated interferon-alfa-2a and other interferons. This serious risk also applies to TYZEKA ® (telbivudine) oral solution and is reflected in your Medication Guide.

Your proposed REMS, submitted on February 27, 2009, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS that was included in your February 27, 2009 submission. The timetable you submitted is as follows:

1st FDAAA assessment:	July 2010 (18 months post-approval)
2nd FDAAA assessment:	January 2012 (3 years post-approval)
3rd FDAAA assessment:	January 2016 (7 years post-approval)

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risk of peripheral neuropathy, as well as previously identified safety risks for TYZEKA®, including lactic acidosis, hepatomegaly, steatosis, myopathy, and worsening of hepatitis B.
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.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 22-154 REMS Assessment
NDA 22-154 Proposed REMS Modification

If you do not submit electronically, please send 5 copies of submissions containing REMS assessments or proposed modifications of the REMS.

Please note that:

- This Medication Guide must be reprinted immediately following the last section of labeling or, alternatively, accompany the prescription drug labeling [21 CFR 201.57 (c)(18)] or 21 CFR 201.80(f)(2)];

- You are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208.24];

- The final printed Medication Guide distributed to patients must conform to all

conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- You are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide is provided [21 CFR 208.24(d)].

PROMOTIONAL MATERIALS

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

HEALTH CARE PROVIDER LETTER

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
Food and Drug Administration
Suite 12B05
5600 Fisher Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kenny Shade, Senior Regulatory Health 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: Package Insert, Medication Guide, Carton and Container labels and REMS document

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

/s/

Kendall Marcus

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