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RESEARCH**

APPLICATION NUMBER:

22-011

APPROVAL LETTER



Food and Drug Administration
Rockville MD 20857

NDA 22-011

Idenix Pharmaceuticals, Inc.
David H. Hallinan, PhD, Vice President, Regulatory Affairs
60 Hampshire Street
Cambridge, MA 02139

Dear Dr. Hallinan:

Please refer to your new drug application (NDA) dated December 30, 2005, received December 30, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TyzekaTM (telbivudine) 600 mg film coated tablets.

We acknowledge receipt of your submissions dated February 13, 2006, February 21, 2006, February 22, 2006, March 3, 2006, March 23, 2006, March 27, 2006, April 18, 2006, April 28, 2006, May 2, 2006, May 11, 2006, May 18, 2006, May 31, 2006, June 7, 2006, July 12, 2006, August 18, 2006 August 28, 2006, September 14, 2006, September 15, 2006, September 25, 2006, September 28, 2006, October 4, 2006, October 12, 2006, October 16, 2006, October 18, 2006, October 23, 2006, October 24, 2006 and October 25, 2006.

This new drug application provides for the use of TyzekaTM (telbivudine) 600 mg film coated tablets for treatment of chronic hepatitis B (CHB) in patients with evidence of viral replication and active liver inflammation.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed labeling text and patient labeling.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert and patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-011.**" Approval of this submission by FDA is not required before the labeling is used.

Submit 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 in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

We acknowledge your commitment to participate in the Antiretroviral Pregnancy Registry.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for birth to 16 years of age until such studies can be conducted. We will issue a formal pediatric written request to you.

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

1. Deferred pediatric study/substudy under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 years of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from birth through 16 years of age to support dose-selection for the efficacy and safety assessment.
2. Deferred pediatric study under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 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.

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

In addition, we note the following postmarketing study commitments, specified in your submission dated October 23, 2006. These commitments are listed below.

Clinical

1. Complete and submit the final study report for Study NV-02B-007, the 104-Week, Phase 3 registrational trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with HBeAg-positive and HBeAg-negative chronic hepatitis B and compensated liver disease.

Protocol submission: Study Ongoing
Final report submission: July 2007

2. Conduct and submit a final study report to evaluate the use of LdT in the treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (Blacks/African Americans, Hispanics).

Protocol submission: June, 2007
Final report submission: June 2010

3. Conduct and submit a final study report for an efficacy and safety study of telbivudine in subjects who are coinfectd with HIV and HBV. This study should include analysis of virologic, biochemical, and serologic endpoints for both HIV and HBV. It should also include evaluation of safety, and evaluation of HBV and HIV resistance.

Protocol submission: June, 2007
Final report submission: June 2010

4. Complete and submit the final study report for Study NV-02B-011, the double-blind trial comparing the efficacy and safety of telbivudine to lamivudine in subjects with chronic hepatitis B and decompensated liver disease.

Protocol submission: Study Ongoing
Final report submission: April 2010

5. Complete and submit the final study report for Study NV-02B-018, the open-label trial comparing the efficacy and safety of telbivudine to adefovir dipivoxil in subjects with HBeAg-positive compensated chronic hepatitis B.

Protocol submission: Study Ongoing
Final report submission: June 2007

6. Complete and submit the final study report for Study NV-02B-022, the open-label, non-comparative trial assessing the long-term antiviral efficacy and safety of telbivudine in subjects with HBeAg-positive and HBeAg-negative compensated and decompensated chronic hepatitis B that have been previously treated in Idenix-sponsored telbivudine studies.

Protocol submission: Study Ongoing
Final report submission: May 2012

Clinical Pharmacology

7. Conduct and submit a final study report for a study evaluating CYP induction potential for telbivudine using in vitro or in vivo studies.

Protocol submission: January 2007

Final report submission: January 2008

8. Conduct and submit a final study report(s) for in vitro studies to evaluate if telbivudine is a P-gp inhibitor.

Protocol submission: January 2007

Final report submission: January 2008

Microbiology

9. Conduct and submit a final study report for a study to determine the anti-HBV cell culture combination activity relationships of telbivudine with entecavir.

Protocol submission: December 2006

Final report submission: April 2007

10. Conduct and submit a final study report for a study to determine the anti-HBV combination activity relationships of telbivudine in cell culture with the HIV NRTIs abacavir, emtricitabine, lamivudine, tenofovir, zalcitibine, and zidovudine.

Protocol submission: February 2007

Final report submission: November 2007

11. Conduct and submit a final study report for a study to determine the susceptibility to telbivudine and adefovir of the HBV rtA181 variants, rtA181T and rtA181S.

Protocol submission: Study Ongoing

Final report submission: November 2007

12. Conduct and submit a final study report for a study to determine the susceptibility in cell culture of HBV harboring the following mutations of highly conserved amino acid residues among HBV isolates: R22C, W58G, L69P, L82M, P99L, L180M, L209V, T240I, I254F, P261L, G295E, A307V, L331F, or A342T. These amino acid substitutions were found in the viruses of patients who experienced virologic failure (serum HBV DNA levels $\geq 1,000$ copies/mL at Week 52) to telbivudine therapy.

Protocol submission: February 2007

Final report submission: February 2008 and December 2009

13. Conduct and submit a final study report for a study to determine the mitochondrial toxicity of telbivudine in growing muscle cells, cell lines and primary cells, and primary hepatocytes with appropriate controls to validate the results.

Protocol submission: March 2007

Final report submission: March 2008

14. Complete and submit a final study report for ongoing genotypic and phenotypic analyses of HBV DNA from patients who experience virologic failure to long-term telbivudine therapy (serum HBV DNA levels $\geq 1,000$ copies/mL) in ongoing clinical trials.

Protocol submission: Study Ongoing (NV-02B-007)

Final report submission: July 2007 update for NV-02B-007 and then annually for those NV-02B-007 patients who roll-over to NV-02B-022 (July 2008 and July 2009).

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b) (2) (vii) and 314.81(b) (2) (viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **“Postmarketing Study Commitment Protocol”, “Postmarketing Study Commitment Final Report”, or “Postmarketing Study Commitment Correspondence.”**

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

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

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely,

(See appended electronic signature page)

Edward Cox, M.D.
Acting Director
Office of Antimicrobial Products
Center for Drug Evaluation and
Research
Food and Drug Administration

Enclosure: approved draft labeling and patient package insert

**This is a representation of an electronic record that was signed electronically and
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/s/

Jeffrey Murray
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