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APPLICATION NUMBER:

22-011

MICROBIOLOGY REVIEW

DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

MICROBIOLOGY REVIEW

NDA: 22011 SN: 000 DATE REVIEWED: 10/23/06

Microbiology Reviewer: Sung S. Rhee, Ph.D.

NDA #: 22011

Serial #: 000

Applicant Name and Address: Idenix Pharmaceuticals, Inc.
60 Hampshire Street
Cambridge, MA 02139

Reviewer's Name(s): Sung S. Rhee, Ph.D.

Initial Submission Dates:

Correspondence Date: December 30, 2005

CDER Receipt Date: December 30, 2005

Reviewer Receipt Date: January 06, 2006

Review Complete Date: October 23, 2006

DAVDP Action Date: October 25, 2006

PDUFA Date: October 30, 2006

Amendments:

Related/Supporting Documents: IND 60459

Product Name(s):

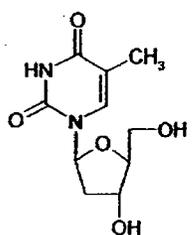
Proprietary: SEBIVO™

Non-Proprietary/USAN: Telbivudine

Code Name/Number: L-dT

Chemical Name: 1-(2-deoxy-β-L-ribofuranosyl)-5-methyluracil

Structural Formula:



Telbivudine

Molecular Formula: C₁₀H₁₄N₂O₅

Molecular Weight: 242.23

Dosage Form(s): 600 mg tablet

Route(s) of Administration: Oral

Indication(s): Treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation

Recommended Dosage: 600 mg once daily

Dispensed: Rx OTC (Discipline relevant)

Abbreviations: A549, human lung carcinoma; ABC, abacavir; ADV, adefovir dipivoxil; ALT, alanine aminotransferase; AZT, zidovudine; BFU-E, burst-forming units-erythroid; CC₅₀, 50% cytotoxic concentration; CFU-GM, colony-forming units-granulocyte-macrophage; CV-1, African green monkey kidney fibroblast cell; Daudi, Burkitt's B cell

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lymphoma; d4T, stavudine; ddC, zalcitabine; ddl, didanosine; DHBV, duck hepatitis B virus; EBV, Epstein Barr virus; EC₅₀, 50% effective concentration; ELISA, enzyme-linked immunosorbent assay; ETV, entecavir; FIAU, fialuridine; FTC, emtricitabine; HBeAg, HBV e antigen; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HFF, human foreskin fibroblast; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IC₅₀, 50% inhibitory concentration; ITT, intent-to-treat; KB, human nasopharyngeal carcinoma; L-dT, telbivudine; LAM, lamivudine; MA-104, Rhesus monkey kidney epithelial cell; MDCK, canine kidney epithelial cell; mtDNA, mitochondrial DNA; NRTI, nucleoside reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; QS, quantitation standard; RT, reverse transcriptase; PDH, primary duck hepatocyte; RSV, respiratory syncytial virus; TFV, tenofovir; VZV, varicella zoster virus; WHsAg, woodchuck hepatitis virus serum antigen; WHV, woodchuck hepatitis virus; ZDV, zidovudine

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EXECUTIVE SUMMARY

Telbivudine, a synthetic thymidine nucleoside analog, demonstrated inhibitory activity against hepatitis B virus (HBV) replication with EC_{50} and EC_{90} values of 0.19 μ M and 0.98 μ M, respectively, in the HBV stably-transfected human liver HepG2.2.15 cell line. Like other nucleoside analogs, telbivudine is phosphorylated by cellular kinases to the active triphosphate form that can be incorporated into HBV DNA by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine-TP causes DNA chain termination, resulting in inhibition of HBV DNA synthesis. In HepG2.2.15 liver cells, telbivudine inhibited both HBV first (EC_{50} value = $1.308 \pm 1.567 \mu$ M) and second strand synthesis (EC_{50} value = $0.237 \pm 0.206 \mu$ M). In biochemical assays telbivudine-TP inhibited the endogenous human, duck, and woodchuck hepatitis viral DNA polymerase (reverse transcriptase, RT) with IC_{50} values of 1.0 μ M, 0.46 μ M, and $0.24 \pm 0.09 \mu$ M, respectively, while no inhibition was observed with human cellular DNA polymerases α , β , or γ at concentrations up to 100 μ M.

Telbivudine was not cytotoxic to numerous cell lines of human and other mammalian origin at the highest concentration tested (50 to 2,000 μ M), including stationary HepG2.2.15 cells (CC_{50} value >2,000 μ M) and human PBMCs (CC_{50} value >200 μ M). In HepG2 cells exposed to telbivudine at concentrations up to 10 μ M, no appreciable mitochondrial toxicity was observed: no differences were observed in mitochondrial DNA content, lactic acid levels produced, and mitochondrial morphology.

Cell-based drug combination studies showed that the anti-HBV activity of telbivudine was additive in combination with adefovir and was not antagonized by the HIV NRTIs didanosine and stavudine. Telbivudine is not active against HIV-1 (EC_{50} value >100 μ M) and was not antagonistic to the anti-HIV activity of abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, or zidovudine.

Cell-based cross-resistance studies indicated significant cross resistance between lamivudine and telbivudine. Telbivudine was inactive against lamivudine-resistant HBV strains containing either the rM204I mutation or the rL180M/rM204V double mutation (fold changes in EC_{50} values of $\geq 1,000$). However, telbivudine exhibited little to no loss of anti-HBV activity against the rM204V single mutation with the calculated fold changes in EC_{50} values of 1.2 ± 0.4 . HBV containing the adefovir-resistance substitution rA181V showed 3- to 5-fold reduced susceptibility to telbivudine, while HBV containing the adefovir-resistance substitution rN236T remained susceptible to telbivudine.

The Phase III clinical study, Study NV-02B-007, examined the efficacy of telbivudine 600 mg once daily compared to lamivudine (LAM) 100 mg once daily for a treatment period of up to 104 weeks in adults chronically infected with HBV and having compensated liver disease but never treated with LAM or an investigational anti-HBV nucleoside or nucleotide analog. FDA analyses indicated that antiviral efficacy of telbivudine at Week 52 was not inferior to LAM in HBeAg-positive and HBeAg-negative patients, confirming the Applicant's conclusion. HBeAg-positive telbivudine-treated patients achieved a mean serum HBV DNA reduction of $6.44 \pm 2.01 \log_{10}$ copies/mL, compared to a mean reduction of $5.46 \pm 2.55 \log_{10}$ copies/mL for LAM-treated patients. In HBeAg-negative

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patients, the mean HBV DNA reductions were $5.18 \pm 1.90 \log_{10}$ copies/mL and $4.37 \pm 2.08 \log_{10}$ copies/mL for telbivudine and LAM, respectively.

In the HBeAg-positive patient population, 65.4% (291/445) of telbivudine recipients were suppressed with serum HBV DNA <1,000 copies/mL and maintained viral suppression by Week 52, compared to 45.9% (209/455) of HBeAg-positive LAM recipients. In the HBeAg-negative patient population, 91.1% (214/235) of telbivudine recipients and 77.6% (180/232) of LAM recipients were suppressed and maintained. More importantly, 57.8% (257/445) of HBeAg-positive telbivudine recipients achieved HBV DNA clearance to PCR nondetectable levels (≤ 300 copies/mL HBV DNA) and maintained viral clearance by Week 52, compared to 37.8% (172/455) of HBeAg-positive LAM recipients. In the HBeAg-negative patient population, maintained HBV DNA clearance to PCR nondetectable levels was achieved by 88.5% (208/235) of telbivudine recipients versus 70.7% (164/232) of LAM recipients.

The rates of virologic failure ($\geq 1,000$ copies/mL at Week 52) and virologic rebound ($\geq 1 \log_{10}$ increase of serum HBV DNA from nadir while on therapy) were lower for telbivudine recipients at Week 52, compared to LAM recipients in both the HBeAg-positive and HBeAg-negative patient populations. For the HBeAg-positive patient population, virologic failure was observed in 33.7% (145/430) of telbivudine recipients versus 53.2% (233/438) of LAM recipients. In the HBeAg-negative patient group, 8.4% (19/227) of telbivudine recipients and 21.5% (48/223) of LAM recipients experienced virologic failure. Virologic rebound was observed in 7.9% (34/430) of telbivudine recipients, compared to 23.5% (233/455) of LAM recipients in the HBeAg-positive patient population, while in the HBeAg-negative patient population, it was observed in 4.9% (11/227) of telbivudine recipients and 16.6% (37/223) of LAM recipients.

Of the 164 patients who showed evidence of virologic failure to telbivudine treatment, the paired amino acid sequences of HBV RT from the screen and on-treatment samples of the 115 evaluable patients were submitted with this application. Amino acid substitutions emerged in the HBV RT from the viruses of 87 patients out of the 115 patients with the average number of changes per patient of 3.4 ± 4.7 (391/115). The 3 most frequently observed changes were at codons 80, 181, and 204 that are highly conserved among HBV isolates. The mutations at codons 80 and 204 have already been associated with both genotypic and phenotypic resistance to LAM, and the mutation at codon 181 to adefovir.

Amino acid substitutions at codon 204 encoding rtM204 were detectable from the viruses of 46 patients (46/115, 40%): HBV variants with the rtM204I substitution were detectable from the viruses of 37 patients (80.4%) and the mixed variants, rtM204M/I or rtM204M/I/V, were present in the HBV DNA of 9 patients (19.6%). No rtM204V mutation, alone or in conjunction with the rtL180M mutation that is strongly associated with LAM resistance developed in response to telbivudine therapy. The rtM204I variants are strongly associated with virologic rebound: 34 patients of the 46 patients whose virus harbored the rtM204I substitution showed evidence of virologic rebound (73.9%). Of 46 patients with the rtM204I substitution, 44 patients had virus that carried other amino acid substitutions in the HBV RT domain. In particular, all patients whose HBV carried mutations at codons 80 (27 patients) or 229 (6 patients) were found to have the rtM204

mutation.

Amino acid substitutions at rtA181 developed in 16 of the 115 patients (13.9%): the mixed rtA181T/A and the pure rtA181T variants were detectable from the viruses of 8 (50%) and 7 patients (43.8%), respectively, and one patient had an rtA181S change. Interestingly, the rtA181V variants, known to confer resistance to ADV and reduced susceptibility to telbivudine in cell culture, were not detected. Of 16 patients, 1 patient also carried the rM204I/M mutation and showed evidence of virologic rebound.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability

This NDA for telbivudine is approvable with respect to microbiology for the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

- Determine the anti-HBV cell culture combination activity relationships of telbivudine with entecavir.
- Determine the anti-HBV combination activity relationships of telbivudine in cell culture with the HIV NRTIs abacavir, emtricitabine, lamivudine, tenofovir, zalcitabine, and zidovudine.
- Determine the susceptibility to telbivudine and adefovir of the HBV rtA181 variants, rtA181T and rtA181S.
- 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.
- 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.
- Continue to perform 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.

2. Summary of OND Microbiology Assessments

2.1. Nonclinical Microbiology

Telbivudine is a synthetic thymidine nucleoside analog and phosphorylated by cellular kinases to the active triphosphate form (telbivudine-TP). Telbivudine-TP has a half-

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life of 14 h in stationary HepG2 cells and can be incorporated into HBV DNA by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine-TP causes DNA chain termination, resulting in inhibition of HBV DNA synthesis.

Telbivudine is an inhibitor of both HBV first and second strand synthesis (EC_{50} values of $1.308 \pm 1.567 \mu\text{M}$ and $0.237 \pm 0.206 \mu\text{M}$, respectively, in stably transfected HepG2.2.15 cells). Telbivudine did not inhibit the HBV priming reaction.

Telbivudine exhibited antiviral activity against HBV in stationary HepG2.2.15 cells, reducing extracellular HBV DNA with EC_{50} and EC_{90} values of $0.19 \mu\text{M}$ ($0.046 \mu\text{g/mL}$) and $0.98 \mu\text{M}$, respectively. The EC_{50} and EC_{90} values of telbivudine against DHBV in primary duck hepatocytes were $0.18 \mu\text{M}$ and $1.0 \mu\text{M}$, respectively.

Telbivudine was not effective against other human viruses tested including human immunodeficiency virus (HIV-1), suggesting that telbivudine is a specific inhibitor for HBV.

Telbivudine-TP did not inhibit human cellular DNA polymerases α , β , or γ in biochemical reactions at concentrations up to $100 \mu\text{M}$.

Telbivudine was not cytotoxic to numerous cell lines of human and other mammalian origin at the highest concentration tested, including stationary HepG2.2.15 cells (CC_{50} value $>2,000 \mu\text{M}$) and human PBMCs (CC_{50} value $>200 \mu\text{M}$). In addition, telbivudine at concentrations of $>10 \mu\text{M}$ had no inhibitory effect on the growth of human bone marrow progenitor cells. No mitochondrial toxicity was observed in HepG2 cells treated with telbivudine at concentrations up to $10 \mu\text{M}$.

Telbivudine exerted additive antiviral effects when combined with adefovir in a stably transfected cell line, HepG2 49-29. No evidence of cytotoxicity or antagonism was observed at the tested concentrations.

Cell-based drug combination studies demonstrated that telbivudine did not enhance or reduce the antiviral efficacy of all seven FDA-approved HIV NRTIs against HIV-1 with the calculated fold changes in EC_{50} values ranging from 0.8- to 1.5-fold. HIV NRTIs didanosine and stavudine exhibited no antagonistic effect on the cell culture antiviral activity of telbivudine against HBV.

2.2. Clinical Microbiology

In Study NV-02B-007, antiviral efficacy of telbivudine (600 mg once daily) was compared to lamivudine (100 mg once daily) separately in the HBeAg-positive and HBeAg-negative patient populations.

At Week 52, HBeAg-positive telbivudine-treated patients achieved a mean serum HBV DNA reduction of $6.44 \pm 2.01 \log_{10}$ copies/mL, compared to a mean reduction of $5.46 \pm 2.55 \log_{10}$ copies/mL for lamivudine-treated patients. In HBeAg-negative patients,

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In the paired sequence analysis of baseline and on-treatment samples, 75.7% (87/115) of patients with evidence of virologic failure had genotypic changes in the HBV reverse transcriptase, including amino acid substitutions rL80I/V, rL180M, rA181T, rM204I, and rL229W/V. All patients whose virus carried mutations at codons 80 (27 patients), 229 (6 patients), or 180 (4 patients) were found to have the rM204 substitution.

Of the 115 patients receiving telbivudine with virologic failure whose paired baseline and on-treatment genotypes were submitted with this application, 46 patients (40.0%) had mutations at codon 204, rM204. The rM204I variants were detectable by population nucleotide sequence analysis in the viruses from 37 patients (80.4%), and the mixed variants, rM204M/I or rM204M/I/V, were detectable in the HBV DNA from 9 patients (19.6%). There was no emergence of the rM204V substitution in response to telbivudine therapy. The mutation profile for telbivudine in the subset of patients with the rM204 mutation is similar to that for lamivudine with the exception of the rM204V mutation.

Sixteen patients (13.9%) of the 115 patients had mutations at codon 181, rA181: the mixed variants, rA181T/A, were detectable from the viruses of 8 patients (50.0%),

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and the rtA181T and rtA181S variants were of 7 (43.8%) and of 1 (6.3%) patients, respectively. No variants with rtA181V were detected.

3. Administrative

3.1. Reviewer's Signature(s)

Sung S. Rhee, Ph.D.
Microbiologist

3.2. Concurrence

HFD-530/Assoc Dir/J. Farrelly

Date: _____

HFD-530/MicroTL/J. O'Rear

Date: _____

CC:
HFD-530/NDA # 22011
HFD-530/Division File
HFD-530/PM/K. Shade



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/s/

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