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*APPLICATION NUMBER:*

**22-011**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

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NDA: 22011	Submission Date(s): Dec 30, 2005
Brand Name	Tyzeka
Generic Name	Telbivudine
Primary Reviewer	Jenny H. Zheng, Ph.D.
Team Leader	Kellie Reynolds, Pharm.D.
PM Team Leader	Jogarao Gobburu, Ph.D.
QT Secondary Reviewer	Christine Garnett, Ph.D.
OCP Division	Division 4
ORM division	DAVP
Applicant	Idenix Pharmaceuticals, Inc.
Relevant IND(s)	IND 60459
Submission Type	Standard
Formulation; Strength(s)	600 mg tablets
Indication	Treatment of chronic hepatitis B infection in adults

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## 1. EXECUTIVE SUMMARY

Telbivudine, a synthetic thymidine nucleoside analogue, is proposed for treatment of HBV infection. Telbivudine 600 mg once daily was studied in adult patients with HBeAg-positive and HBeAg-negative chronic hepatitis B infection. In HBeAg-positive patients, telbivudine was superior to lamivudine in Therapeutic Response. In HBeAg-negative patients, telbivudine was non-inferior to lamivudine. Telbivudine was generally well tolerated, with most adverse experiences classified as mild or moderate in severity and similar to lamivudine.

### 1.1 Recommendation

The Clinical Pharmacology and Biopharmaceutics information provided by the applicant is acceptable. The outstanding issues that need to be addressed are listed in the Phase IV Commitments section.

### 1.2 Phase IV Commitments

- Evaluate CYP induction potential for telbivudine using in vitro or in vivo studies. (protocol submission- January 2007, final report submission- January 2008)\*
- Conduct in vitro studies to evaluate if telbivudine is a P-gp inhibitor. (protocol submission- January 2007, final report submission- January 2008)

\* The applicant proposed to conduct an in vitro study, which is acceptable. However, if the in vitro study shows there is an induction, in vivo study may be needed.

### 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Telbivudine ( $\beta$ -L-2'-deoxythymidine; LdT) is a synthetic thymidine nucleoside analogue proposed for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and active liver disease. Following intracellular phosphorylation to the active metabolite (LdT-5'-triphosphate), the drug inhibits HBV DNA polymerase, and consequently, viral replication. Telbivudine triphosphate has an intracellular half-life of 14 hours. The concentration of telbivudine that effectively inhibited 50% of viral DNA synthesis ( $EC_{50}$ ) in the HBV-expressing human hepatoma cell line 2.2.15, as well as in primary duck hepatocytes infected with duck hepatitis B virus was approximately 0.2  $\mu$ M (50 ng/mL).

The clinical pharmacology of telbivudine has been characterized in healthy and HBV-infected subjects, as well as *in vitro* studies. These studies show telbivudine demonstrates the following clinical pharmacology and biopharmaceutical characteristics:

- Dose-response data from the Phase I/IIa dose-finding trial [NV-02B-001] using Emax model predicted that the maximal achievable antiviral efficacy for telbivudine occurs in the 400-800 mg/d dosing range. Data from the Phase IIb trial [NV-02B-003] indicated that the 400 mg and 600 mg daily doses provided similar antiviral efficacy. To maximize antiviral efficacy and reduce the emergence of viral resistance, a dose of 600 mg/d was chosen for the Phase III program. This dose (600 mg/d) was selected based on both the Emax model, which predicted approximately a 0.2 log<sub>10</sub> (~40%) greater antiviral effect over the 400 mg/d dose, and the NV-02B-001 and NV-02B-003 safety observations, which indicated a lack of dose-related safety concerns. A higher dose is not expected to provide better efficacy.

- There is no effect on QTcf interval after treatment with telbivudine at either the clinical dose (600 mg/day) or the supra-therapeutic dose (1800 mg/day) in a thorough QT study. There was no increase in QTcf with increasing plasma telbivudine concentration.
- Following oral administration, telbivudine peak plasma concentrations (C<sub>max</sub>) occurred between 1 and 6 hours (median 3 hours).
- Following multiple once daily doses or single dose ranging from 200 mg to 800 mg, area under the concentration-time curve (AUC) at steady state increased less than proportionally to dose.
- For telbivudine 600 mg once daily (n = 12), steady-state C<sub>max</sub> was 3.69 ± 1.25 µg/mL (mean±SD), AUC was 26.1 ± 7.2 µg·h/mL (mean±SD), and trough plasma concentrations (C<sub>trough</sub>) were approximately 0.2-0.3 µg/mL, which is 3-5 fold higher than the EC<sub>50</sub> of telbivudine (0.05 µg/mL).
- Telbivudine exhibits a long plasma terminal elimination half life (~40 hours). Steady state was achieved after 5 to 11 days of once-daily administration with approximately 1.5-fold accumulation, suggesting an effective half-life of approximately 15 hours.
- Telbivudine absorption and exposure were unaffected when a single 600 mg dose was administered with a high-fat (~55 g), high-calorie meal (~950 kcal) meal. Telbivudine may be taken with or without food.
- Telbivudine has low plasma protein binding (3.3%). After oral dosing, the estimated apparent volume of distribution is in excess of total body water, suggesting that telbivudine is widely distributed into tissues. Telbivudine was equally partitioned between plasma and blood cells.
- No metabolites are found in human biological matrices including plasma, urine and feces.
- Systemic telbivudine is primarily excreted unchanged in urine. Approximately 42% of the dose is recovered in the urine over 7 days following a single 600 mg oral dose of telbivudine.
- Telbivudine exhibits renal function-dependent pharmacokinetics and dose interval adjustment is recommended in patients with moderate to severe renal impairment, including patients with ESRD on hemodialysis (CLCR < 50 mL/min). Within 2 hours following a single 200 mg dose of telbivudine, a 4-hour hemodialysis session removed approximately 23% of the telbivudine dose.
- The pharmacokinetics of telbivudine are not affected by age, gender, race, or underlying disease (HBV infection).
- Telbivudine pharmacokinetics are not significantly altered by impaired hepatic function.
- Telbivudine does not inhibit human hepatic CYP450 activities. However, CYP450 induction potential for telbivudine was not studied.
- Drug-drug interaction studies show that lamivudine, adefovir dipivoxil, cyclosporine and pegylated interferon-alfa 2a do not alter telbivudine pharmacokinetics. In addition, telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, or cyclosporine. No definitive conclusion could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations.
- Telbivudine is not a P-gp substrate based on the in vivo cyclosporine drug-drug interaction study. However, the potential for P-gp inhibition was not evaluated.

Overall, the cumulative data regarding the clinical pharmacology of telbivudine support the proposed use of this drug in the treatment of patients with chronic hepatitis B.

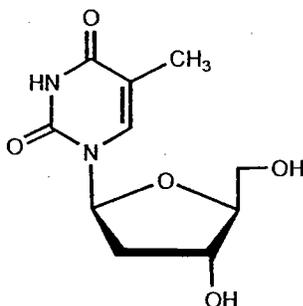
## 2. QUESTION BASED REVIEW

### 2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The structure and physical properties of telbivudine are shown below:

Structural formula:



Chemical Name: 1-(2-deoxy- $\beta$ -L-ribofuranosyl)-5-methyluracil  
 Molecular Weight: 242.23  
 pH-solubility profile: Telbivudine is sparingly soluble in water (20 mg/mL) and in the pH range of 4.0 to 9.0.  
 PKa:  $9.61 \pm 0.01$   
 Log P (partition coefficient) of telbivudine:  $-1.35 \pm 0.10$  in octanol/water  
 Apparent Permeability: medium permeable (10 -30 nm/sec)

The quantitative composition of the to-be-marketed telbivudine tablets are shown in the following table:

Ingredient <sup>1)</sup>	Amount per film coated tablet [mg]	Function	Reference to standards
<b>Tablet core</b>			
<b>Inner phase</b>			
Telbivudine (LDT600)			Novartis monograph
Cellulose microcrystalline / Microcrystalline cellulose			Ph. Eur. / NF
Povidone			Ph. Eur. / USP
Sodium starch glycolate (type A) / Sodium starch glycolate			Ph. Eur. / NF
Water purified / Purified water <sup>2)</sup>			Ph. Eur. / USP
<b>Outer phase</b>			
Cellulose microcrystalline / Microcrystalline cellulose			Ph. Eur. / NF
Sodium starch glycolate (type A) / Sodium starch glycolate			Ph. Eur. / NF
Magnesium stearate <sup>3)</sup>			Ph. Eur. / NF
Silica, colloidal anhydrous / Colloidal silicon dioxide			Ph. Eur. / NF
<b>Total core weight</b>	-		
<b>Coating</b>			
Basic coating premix white <sup>4)</sup>	-		Novartis monograph
Water purified / Purified water <sup>2)</sup>	-		Ph. Eur. / USP
<b>Total film-coated tablet weight</b>	<b>842.0</b>		

1) Both the Ph.Eur. and the USP/NF names of ingredients are provided as applicable; 2 )

### 2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours. Telbivudine 5'-triphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine 5'-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication.

Telbivudine is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

### 2.1.3. What are the proposed dosage(s) and route(s) of administration?

The recommended dose of telbivudine for the treatment of chronic hepatitis B is 600 mg (one 600 mg tablet) once daily, taken orally, with or without food. The optimal treatment duration has not been established.

Telbivudine may be used for the treatment of chronic hepatitis B in patients with impaired renal function. No adjustment to the recommended dose of telbivudine is necessary in patients whose creatinine clearance is  $\geq 50$  mL/min. Adjustment of dose interval is required in patients with creatinine clearance  $< 50$  mL/min including those with ESRD on hemodialysis as shown in the following table. For patients with ESRD, telbivudine should be administered after hemodialysis.

<b>Creatinine clearance (mL/min)</b>	<b>Dose of Telbivudine</b>
$\geq 50$	600 mg once daily
30 – 49	600 mg once every 48 hours
$< 30$ (not requiring dialysis)	600 mg once every 72 hours
ESRD	600 mg once every 96 hours

No adjustment to the recommended dose of telbivudine is necessary in patients with hepatic impairment.

## **2.2 General Clinical Pharmacology**

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The dose selection for telbivudine pivotal clinical trials was based on results from a 4-week Phase I/IIa dose-finding trial (NV-02B-001) in adults with HBeAg-positive chronic hepatitis B. The safety, pharmacokinetics and preliminary antiviral activity of telbivudine (LdT) were determined at doses of 25, 50, 100, 200, 400 and 800 mg QD. Dose-response data from this study supported the selection of 600 mg once daily as the preferred telbivudine dose to be further evaluated in the clinical development program. The dose selection was supported by the Phase IIb study (NV-02B-003), which shows that the efficacy and safety for telbivudine 400 mg and 600 mg daily doses are similar. A renal impairment study (Study NV-02B-006) and a population pharmacokinetic analysis (Study # NV-02B-PPK) support the dosing interval adjustment for patients with reduced renal functions.

Efficacy of telbivudine and the approval of telbivudine are mainly based on a large global Phase III trial, NV-02B-007. The study included the HBeAg-positive and HBeAg-negative

patient populations in a pre-stratified manner, with lamivudine as the active control. The study duration is 2 years and the primary (Week 52) data analysis has been completed. The Phase IIb dose confirmation trial NV-02B-003 also supports the overall efficacy claim. Two-year data from the extension trial [NV-02B-010] as well as partial Week 76 data from the pivotal trial NV-02B-007 are used to demonstrate continued benefits with treatment, beyond the first year.

In total, 760 subjects have been treated with telbivudine in clinical studies at a dose of 600 mg once daily. Assessment of adverse reactions is primarily based on the pivotal global Phase III trial, NV-02B-007, in which 1367 patients with chronic hepatitis B received double-blind treatment with telbivudine 600 mg/day (n=680 patients) or lamivudine (n=687 patients) for up to 104 weeks. Median duration of treatment in study NV-02B-007 was 60 weeks for telbivudine- and lamivudine-treated patients. The safety profiles of telbivudine and lamivudine were generally comparable in this study.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The proportion of subjects with therapeutic response was the primary measure of efficacy in the pivotal Phase III study (NV-02B-007). Therapeutic response was defined as HBV DNA <5 log<sub>10</sub> copies/mL with either HBeAg loss or ALT normalization at Week 52. The key secondary endpoint in NV-02B-007 was histologic response, which was defined as improvement (≥2-point decrease) in the Knodell necroinflammatory score with no worsening of fibrosis (worsening was defined as ≥1-point increase in the Knodell fibrosis score) at the Week 52 liver biopsy compared with baseline. The primary efficacy endpoint in the Phase I/II study, (NV-02B-001) was Virologic Response rate (HBV DNA reduction ≥2 log<sub>10</sub> copies/mL from baseline) at Week 4. The primary efficacy endpoint for the Phase IIb study (Study NV-02B-003) was HBV DNA reduction, defined as log<sub>10</sub> HBV DNA reduction from Weeks 1 to 12 as assessed by the AUCMB method, in which AUCMB is the normalized area-under-the-curve minus Baseline.

Historically, the Division of Antiviral Products (DAVP) has required histologic endpoints in the analysis of efficacy of drugs for treatment of chronic HBV. Improvement in liver histology has been considered a surrogate for the true endpoints, development of HBV-related complications (cirrhosis, liver transplantation, hepatocellular carcinoma) and death.

In August, 2002, the DAVP convened an issue-oriented Advisory Committee to discuss the design of clinical trials for treatment of HBV and the appropriate efficacy endpoints to be considered for drug approval. At that time, extensive statistical evaluation of data generated during the lamivudine and adefovir clinical trials was presented. These data showed poor capacity of virologic (HBV DNA levels) and biochemical (ALT levels) endpoints to predict improvement in liver histology after 48 weeks of treatment. The lack of correlation was interpreted by some on the Advisory Committee to suggest that virologic and biochemical measures might not correlate well with clinical outcome, but it was also noted that it is possible that the inflammatory score does not actually correlate with clinical outcomes and that the virologic and biochemical markers do correlate with clinical outcome. The limitations of liver biopsy were identified including: risks of the procedure, subjects' hesitation to undergo the procedure, difficulty in obtaining an

adequate and representative sample of liver tissue, and limitations on the number of time-points at which samples can be obtained. The possible use of a composite efficacy endpoint as a primary efficacy endpoint in future trials was discussed. Some Advisory Committee members were leaning more towards a composite endpoint (e.g. combination of virologic, biochemical and or serologic endpoints), while others advocated for maintaining the primacy of a primary histologic endpoint. The Committee acknowledged that neither a histologic endpoint nor a composite endpoint is a perfect measure of efficacy and that neither is proven to correlate with clinical outcome. There appeared to be consensus, however, among Committee members that the population being treated and the goals of therapy should, at least partially, influence the selection of the primary endpoint.

Between February 2002 and October 2002, the Applicant and the Division engaged in a series of written and telephone-based discussions regarding the selection of an appropriate primary efficacy endpoint for the Phase III registrational trial. In a teleconference between the Division and the Applicant on October 30, 2002, the two parties agreed that histology could be acceptable as an extremely important secondary efficacy endpoint as long as an appropriate plan to obtain paired biopsy specimens from a significant majority of patients, which were representative of the study demographics. Therefore, therapeutic response was chosen as a primary endpoint and histologic response as a key secondary endpoint.

#### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Telbivudine concentrations in human plasma and urine samples were determined by validated liquid chromatographic methods using LC/MS/MS. The assays are acceptable. See section 2.6 for further details.

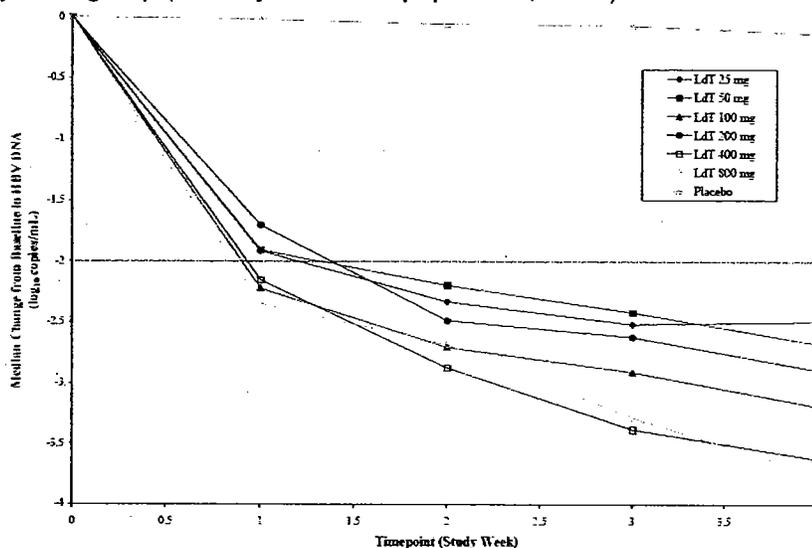
#### 2.2.4 Exposure-response

Results from one randomized, blinded, dose-finding study (NV-02B-001) were used as the initial basis for defining a dose range of telbivudine that was efficacious and well-tolerated. This study was followed by a controlled, randomized, parallel group dose-confirmation study (NV-02B-003) with a primary efficacy endpoint of reduction in HBV DNA (as measured by AUC) by Week 12 to compare the antiviral efficacy of two doses of telbivudine (400 and 600 mg once daily). Dose-response data from the Phase I/IIa dose-finding trial [NV-02B-001] using Emax model predicted that the maximal achievable antiviral efficacy for telbivudine occurs in the 400-800 mg/d dosing range. Data from the Phase IIb trial [NV-02B-003] indicated that the 400 mg and 600 mg daily doses provided similar antiviral efficacy. To maximize antiviral efficacy and reduce the emergence of viral resistance, a dose of 600 mg/d was chosen for the Phase III program. This dose (600 mg/d) was selected for the Phase III trials based on the Emax model, which predicted approximately a 0.2 log<sub>10</sub> (~40%) greater antiviral effect over the 400 mg/d dose, and the NV-02B-001 and NV-02B-003 safety observations, which indicated a lack of dose-related safety concerns. The detailed exposure-response findings for telbivudine are presented in sections 2.2.4.1 and 2.2.4.2 below.

##### *2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

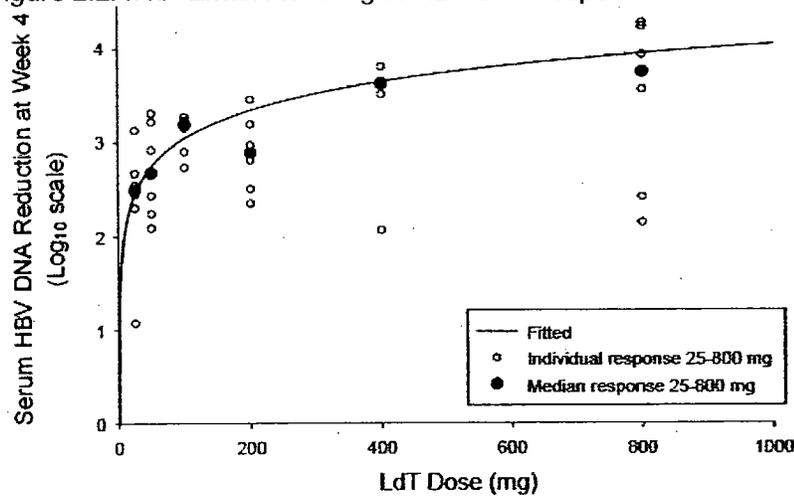
The results of study NV-02B-001 demonstrate that telbivudine administered daily for four weeks, at doses ranging from 25 mg to 800 mg/d, had potent anti-HBV activity as demonstrated by the Virologic Response rate (HBV DNA reduction  $\geq 2$  log<sub>10</sub> copies/mL) at Week 4 of 97% for telbivudine recipients compared to 0% for placebo recipients ( $p < 0.0001$ ). In all telbivudine dose groups, mean and median decreases in HBV DNA of  $> 2$  log<sub>10</sub> copies/mL were seen by Week 2 and were sustained through Week 4. Figure 2.2.4.1a displays median change from Baseline in HBV DNA during the treatment period (Weeks 1 through 4), by dose group.

Figure 2.2.4.1a: Median change from baseline in HBV DNA (log<sub>10</sub> copies/mL) through week 4, by dose group (efficacy evaluable population; N=41)



The relationship between telbivudine dose and virologic response (HBV DNA reduction) was further examined in the data from this study, by an Emax modeling approach. The Emax model estimate for ED<sub>50</sub> was 0.09 mg (S.E. 0.01). The conformity of the HBV DNA data from this study, by dosing group, to the fitted Emax curve is illustrated in Figure 2.2.4.1b. The data show that antiviral activity was dose-proportional for the doses less than 400 mg/d. There was a diminishing increment in HBV DNA reduction for daily doses above this dose, with a plateau in HBV DNA reduction reached between the two highest dose groups tested (400 mg/d and 800 mg/d). The median reductions in HBV DNA were 3.63 log<sub>10</sub> and 3.75 log<sub>10</sub> copies/mL, respectively for the 400 mg/d and 800 mg/d dose groups at the end of four weeks of treatment. The dose-response (Emax) analyses indicate that a telbivudine dose of 600 mg/day will provide near-maximal antiviral activity (about 0.2 log<sub>10</sub> greater than the 400 mg dose, and only 0.1 log<sub>10</sub> less than the 800 mg dose).

Figure 2.2.4.1b Emax modeling of HBV DNA response at Week 4



Because plasma concentrations were not measured in the Phase IIb and Phase III studies and blood sampling time in the Phase Ib/IIa study is short (8 hours) as compared to its effective half-life (14 hours, to estimate  $AUC_{inf}$  after single dose) or dosing interval (24 hours, to estimate steady-state  $AUC$ ), no exposure-response relationship was assessed for telbivudine.

*2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

Telbivudine has been studied up to 1800 mg in healthy subjects and up to 800 mg in patients. Telbivudine is generally safe and tolerable. In study NV-02B-001, no clear treatment-related pattern was seen with regard to the occurrence of adverse events overall or drug-attributed adverse events. Within the limitations of the relatively small cohort sizes used in this study, no clear dose-related pattern was seen with regard to the incidence of specific types of adverse events among the treatment groups. Therefore, no dose-limiting toxicities were identified for telbivudine treatment in this study in the tested dosing range from 25 to 800 mg/day for four weeks. The clinical AEs seen in another dose-ranging study NV-02B-003 were similar to the results obtained from Study NV-02B-001.

In the Phase III study (NV-02B-007), more common creatine kinase (CK) elevations have been identified in telbivudine treatment arm (72%) as compared to lamivudine treatment arm (42%), and more ALT flares were observed among subjects on lamivudine. Most subjects with CK elevations did not report muscular symptoms. There are some rare cases of myopathy (0.5%) have been identified in Phase III trials with 600 mg QD. These patients recovered after study drug discontinuation. Whether myopathy is increased with doses or exposure is unknown.

*2.2.4.3 Does this drug prolong the QT or QTc interval?*

A thorough QT study was conducted for telbivudine. This study met the criteria for a negative, thorough QT study. Telbivudine, at a clinical dose of 600 mg and a supra-therapeutic dose of 1800 mg, was negative and moxifloxacin was positive for QTc prolongation.

This was a phase I, randomized, partially single-blinded, placebo and active (moxifloxacin) controlled, four-period crossover study. All subjects were randomized to one of four treatment sequences of two telbivudine doses, moxifloxacin, and placebo, with a two-week washout period between treatments. Both telbivudine doses (600 and 1800 mg) and placebo were administered for 7 days; moxifloxacin (400 mg) was administered only on Day 7.

The study shows that uncorrected QT in placebo subjects is decreased with increased heart rate, while Bazett's corrected QT (QTcB) increased with increased heart rates. Frederica's corrected QT (QTcF) is constant with increase heart rates, and thus is the best measurement for QT.

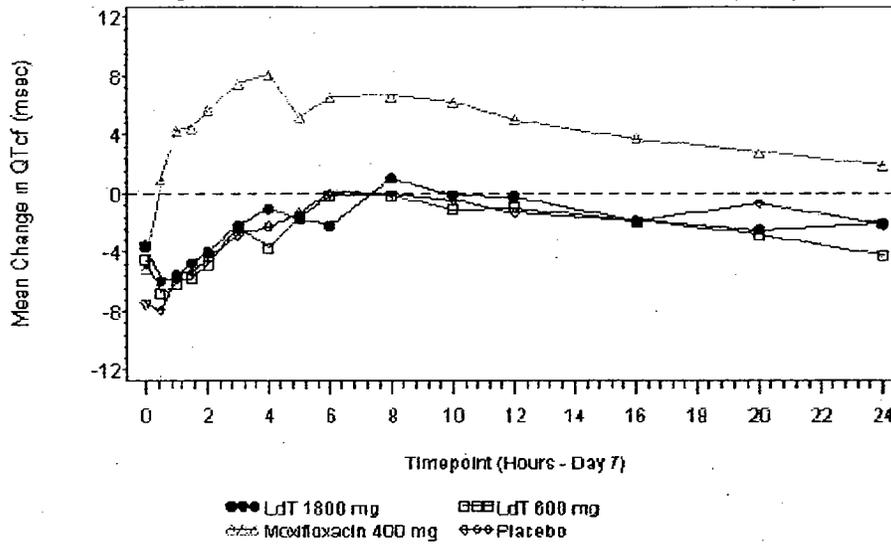
The 15 time-matched placebo-adjusted changes from baseline at Day 7 demonstrated that neither telbivudine 600 mg nor telbivudine 1800 mg exceeded the threshold of 10 msec for the upper limit of the 95% confidence interval (CI) at any timepoint and that the changes were relatively consistent between the dose groups. The effect of positive control, moxifloxacin, on QTc is positive (lower limit of the 95% CI for the maximum effect is more than 5 msec) and is within the range of reported values in the literature. The plots by treatment group demonstrate that the telbivudine treatment groups and placebo had a similar profile over time (h) for Day 7, suggesting that there is no effect on QTcF interval after treatment with telbivudine at either the clinical dose (600 mg/day) or the supra-therapeutic dose (1800 mg/day).

**Summary of time-matched, placebo-adjusted mean change from baseline (msec) in QTcF for Day 7 by treatment group for completed subjects (n=53)**

Time	Moxifloxacin		Telbivudine 600 mg		Telbivudine 1800 mg	
	$\Delta$ QTcF	Upper 95% CI	$\Delta$ QTcF	Upper 95% CI	$\Delta$ QTcF	Upper 95% CI
0 h	1.9	4.4	3.4	5.9	4.4	6.9
0.5 h	7.9	10.7	1.1	3.9	2.4	5.2
1 h	9.3	12.3	-0.7	2.3	-0.4	2.5
1.5 h	8.5	11.4	-0.3	2.6	0.0	2.8
2 h	9.2	12.2	-0.4	2.6	-0.5	2.5
3 h	10.0	13.1	1.3	4.3	0.3	3.4
4 h	9.9	13.0	-0.8	2.2	2.0	5.0
5 h	6.4	9.2	-0.4	2.3	-0.5	2.2
6 h	6.3	9.2	0.1	3.0	-2.5	0.4
8 h	6.9	9.7	-0.1	2.7	1.4	4.2
10 h	6.6	9.6	0.5	3.6	1.4	4.5
12 h	6.6	9.3	1.2	3.9	1.7	4.5
16 h	4.9	7.5	-1.9	0.7	-0.5	2.1
20 h	3.7	6.8	-1.5	1.5	-1.3	1.7
24 h	3.5	6.2	-2.6	0.1	-0.3	2.3

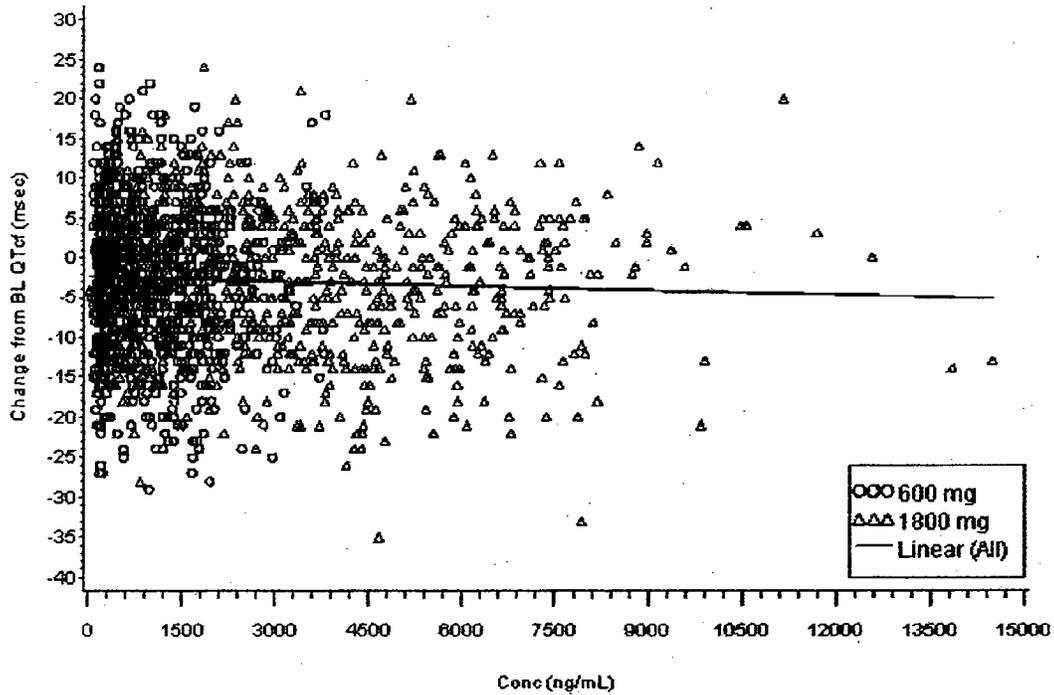
$\Delta$  QTcF: change in QTcF.

Mean change from baseline in QTcf interval by hour for Day 7 by treatment group



There was no increase in QTcf with increasing plasma telbivudine concentration as shown in the following figure.

Mean change from baseline in QTcf interval vs. telbivudine concentration following Day 7 dose (all telbivudine)



*2.2.4.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

For adults and adolescents (>16 years of age), the recommended dose of telbivudine for the treatment of chronic hepatitis B is 600 mg once daily, taken orally, with or without food. As shown in Section 2.2.4.1, the dose and dosing regimen selected by the sponsor is consistent with the known relationship between dose-response. For renally impaired subjects, no adjustment to the recommended dose of telbivudine is necessary in patients whose creatinine clearance is  $\geq 50$  mL/min. Adjustment of dose interval (see Section 2.1.3) is required in patients with creatinine clearance  $< 50$  mL/min including those with ESRD on hemodialysis. For patients with ESRD, telbivudine should be administered after hemodialysis. The dose adjustment is acceptable (see Section 2.3.1).

**2.2.5 What are the PK characteristics of the drug and its major metabolite?**

Telbivudine is not metabolized in humans. The following subsections describe the PK characteristics of telbivudine.

*2.2.5.1 What are the single dose and multiple dose PK parameters?*

The following table summarized the mean (SD) telbivudine PK parameters following administration of single dose of 600 mg telbivudine and the mean (SD) steady-state telbivudine PK parameters following administration of 600 mg telbivudine once daily in healthy subjects (Study NV-02B-016, n = 42). See Section 2.2.5.8 for PK parameters at other doses.

Table 2.2.5.1 PK parameters of telbivudine in healthy subjects

	C <sub>max</sub> (ng/mL)	T <sub>max</sub> *(h)	C <sub>trough</sub> (ng/mL)	AUC <sub>0-∞</sub> /AUC <sub>ss</sub> (ng/mL·h)	T <sub>1/2</sub> (h)
600 mg single dose	3704 (1219)	2.0 (0.5 -3.0)	NA	26441(8938)	39.4 (12.1)
600 mg steady-state	3590 (1247)	2.0 (1.0 -4.0)	252.7 (74.0)	26124 (7196)	48.8 (10.5)

\*median (range)

*2.2.5.2 How does the PK of the drug in healthy volunteers compare to that in patients?*

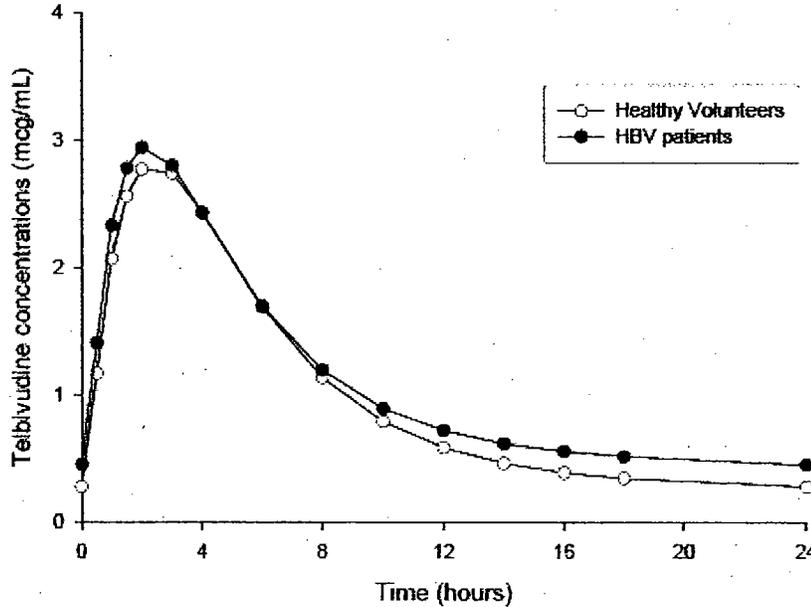
The PK of telbivudine was not studied in patients at 600 mg. The population PK analysis (NV-02B-PPK) based on 25 Phase I study in healthy subjects and 1 Phase I/IIa study in patients, estimated that the telbivudine PK parameters in patients (Table 2.2.5.2) are similar to the PK parameters obtained in healthy subjects (Table 2.2.5.1). Figure 2.2.5.2 shows the predicted steady-state concentration-time profiles for healthy volunteers and HBV infected patients with CLCR  $\geq 50$  mL/min receiving telbivudine 600 mg/day by population PK analysis.

Table 2.2.5.2 Predicted PK parameters of telbivudine in hepatitis B patients

	C <sub>max</sub> (ng/mL)	T <sub>max</sub> *(h)	AUC <sub>ss</sub> (ng/mL·h)	T <sub>1/2</sub> (h)
600 mg single dose	2683 (695)	2.1 (0.8 -4.8)	NA	NA
600 mg steady-state	3251 (866)	2.1 (0.8 -4.1)	31679(15461)	51.4 (18.7)

\*median (range)

Figure 2.2.5.2 Predicted steady-state concentration-time profiles for healthy volunteers and HBV infected patients with CLCR  $\geq$  50 mL/min receiving telbivudine 600 mg/day



#### 2.2.5.3 What are the characteristics of drug absorption?

Following oral administration of 600 mg [14C]-telbivudine, 42% of the dose was recovered unchanged in urine; therefore, the oral bioavailability of telbivudine is  $\geq$ 40%. Peak plasma concentrations ( $C_{max}$ ) of telbivudine occur between 1 and 6 hours after drug administration.

#### 2.2.5.4 What are the characteristics of drug distribution?

*In vitro* binding of telbivudine to human plasma proteins is low (3.3%). The apparent total volume of distribution ( $V_d$ ) estimated by assuming  $F = 40\%$  (NV-02B-009, mass balance study) is 8.2L/kg. These results indicate that the telbivudine  $V_d$  is largely in excess of body water, suggesting that telbivudine is widely distributed into tissues. The mass balance study shows that whole blood and plasma radioactivity mean  $C_{max}$  and AUC values were comparable, indicating that telbivudine was equally partitioned between plasma and blood cells.

	Plasma Radioactivity (mean $\pm$ SD)	Whole blood Radioactivity (mean $\pm$ SD)
$C_{max}$ (ng/mL)	2765 $\pm$ 848	2555 $\pm$ 707
AUC <sub>0-t</sub> (ng.hr/mL)	17765 $\pm$ 5504	16362 $\pm$ 4913

#### 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The mass balance study suggested that telbivudine is eliminated primarily by urinary excretion of unchanged drug. Following oral administration of 600 mg [14C]-telbivudine, an average of 91.6% of the total radioactive dose was recovered in the urine and feces

within 168 hrs after dosing. Urinary recovery and fecal recovery of telbivudine account for 41.9% and 49.6%, respectively. No metabolites of telbivudine were detected in plasma, urine, or feces following administration of [<sup>14</sup>C]-telbivudine in humans. The plasma telbivudine mean C<sub>max</sub> and AUC values of unchanged telbivudine and plasma radioactivity were similar, evidence of absence of circulating plasma metabolites. Telbivudine excreted mostly by passive diffusion (Study NV-02B-006), and it has molecular weight of less than 250 g/mol. Therefore, the possibility of biliary excretion is low.

#### *2.2.5.6 What are the characteristics of drug metabolism?*

No metabolites of telbivudine were detected in plasma, urine, or feces following administration of [<sup>14</sup>C]-telbivudine in humans. Telbivudine is not a substrate, or inhibitor of the cytochrome P450 (CYP450) enzyme system.

#### *2.2.5.7 What are the characteristics of drug excretion?*

The renal clearance of telbivudine approaches normal glomerular filtration rate suggesting that passive diffusion is the main mechanism of excretion. Approximately 42% of the dose is recovered in the urine over 7 days following a single 600 mg oral dose of telbivudine. Because renal excretion is the predominant route of elimination, patients with moderate to severe renal dysfunction and those undergoing hemodialysis require a dose adjustment.

#### *2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

Following oral administration of 200 mg and 800 mg telbivudine in healthy subjects, the AUC of telbivudine increased in less than dose proportional manner (Figure 2.2.5.8a, data from Studies NV-02B-016 and D35001007). Dose proportionality was assessed by a power model. If 95% confidence interval (CI) of the slope in the plot of log (AUC/dose) vs. log (dose) contains 0, AUC is increased in a dose-proportional manner. Figure 2.2.5.8a shows that the mean slope and 95% CI for the slope are less than 0 in both Study NV-02B-016 (Study 016) and Study D35001007 (Study 007).

The applicant would like to claim that "telbivudine pharmacokinetics are dose proportional over the range of 25 mg to 1800 mg", based on a study in hepatitis B infected subjects (Study NV-02B-001) and a thorough QT study (Study NV-02B-024). In Study NV-02B-001, the blood sampling duration was only 8 hours. In addition, an HPLC technique with UV detection was first applied to samples from dose cohorts of 25 to 400 mg. This methodology has a limited sensitivity (LOQ-  ) and has proved to be less adequate for the lower dose cohorts (25 and 50 mg). In the thorough QT study, two doses were studied: the clinical dose 600 mg and a higher dose 1800 mg. The study showed that telbivudine was dose proportional between 600 mg and 1800 mg at steady-state. However, the concentrations for 600 mg dose were 40% lower than other studies (Table 2.2.5.8a).

Figure 2.2.5.8a Dose proportionality evaluation

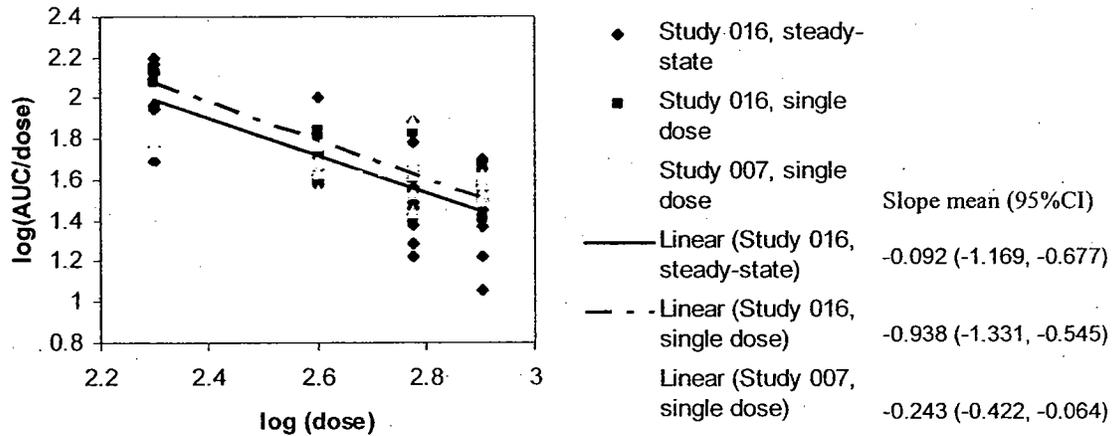


Table 2.2.5.8a Summary of mean telbivudine AUC and Cmax at different doses<sup>a</sup>

Dose (mg)	AUC (µg.hr/mL) <sup>b</sup>				Cmax (µg/mL)			
	Study 016, s.d.	Study 007, s.d.	Study 001 <sup>a</sup> , s.s.	Study 024, s.s.	Study 016, s.d.	Study 007, s.d.	Study 001 s.s.	Study 024, s.s.
25			0.75				0.22	
50			1.60				0.27	
100			4.14				0.61	
200	12.84	10.70	6.67		1.75	1.55	0.99	
400	22.95	18.11	13.42		2.59	2.66	1.80	
600	26.44	27.50		16.5	3.70	3.82		2.2
800	28.82	29.26	29.73		3.46	4.18	3.97	6.6
1800				48.2				

<sup>a</sup> Study 016: Study NV-02B-016; Study 007: Study D35001007; Study 001: Study NV-02B-001; Study 024: Study NV-02B-024

<sup>b</sup> AUC<sub>0-inf</sub> for single dose (s.d.) administration; AUC<sub>ss</sub> for steady-state (s.s.) administration

### 2.2.5.9 How do the PK parameters change with time following chronic dosing?

Clearance of telbivudine does not appear to change following chronic dosing, as demonstrated in Table 2.2.5.1, which shows that AUC<sub>0-∞</sub> after single dose of 600 mg telbivudine and AUC<sub>ss</sub> at steady-state after 600 mg once daily dose are similar.

### 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

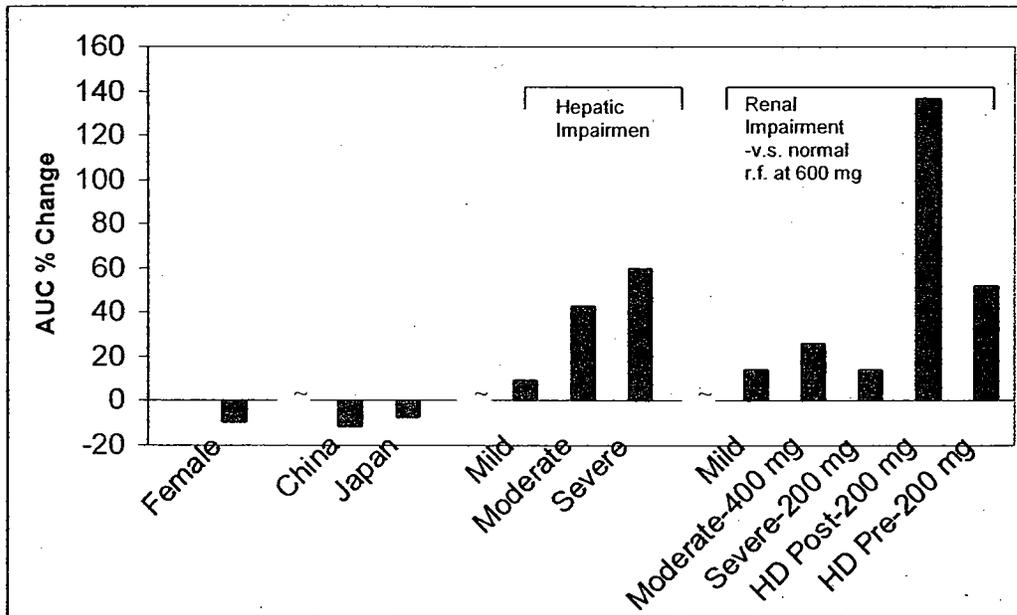
Inter-subject variability (CV%) for measures of systemic exposure (C<sub>max</sub>, AUC) of telbivudine was typically ≤ 30% in all the PK studies. The population PK analysis indicated telbivudine has random error/intra-subject error of 22.4% in concentrations.

## 2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses? What dosage regimen adjustments are recommended for each of these groups?

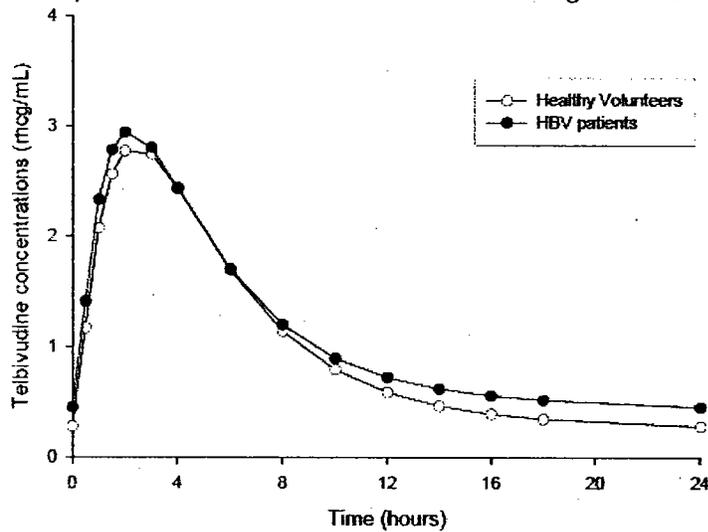
Figure 2.3.1a shows overall comparison of the effect of intrinsic factors from Study NV-02B-004 (Female (test, n=6) vs. male (reference, n=6) at steady-state), Study NV-02B-025 (US as reference for China and Japan, n= 24), Study NV-02B-016 (China, n =42), Study D35001007 (Japan, n= 32), Study NV-02B-006 (n = 36, compared to subjects with normal renal function), and Study NV-02B-005 (n=24, compared to subjects with normal hepatic function). The graph shows that the pharmacokinetics of telbivudine is not significantly affected by gender, race and hepatic impairment, but is affected by renal impairment.

Figures 2.3.1a Overall effect of intrinsic factors on telbivudine exposure based on individual studies (change from the reference, which differs by study)



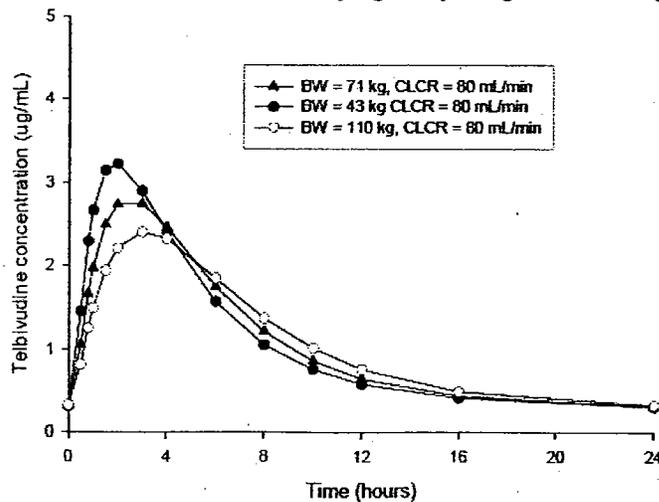
The population PK analyses also suggest that the pharmacokinetics of telbivudine are independent of disease state (Figure 2.3.1b).

Figure 2.3.1b Predicted steady-state concentration-time profiles for healthy volunteers and HBV infected patients with CLCR  $\geq 50$  mL/min receiving telbivudine 600 mg/day



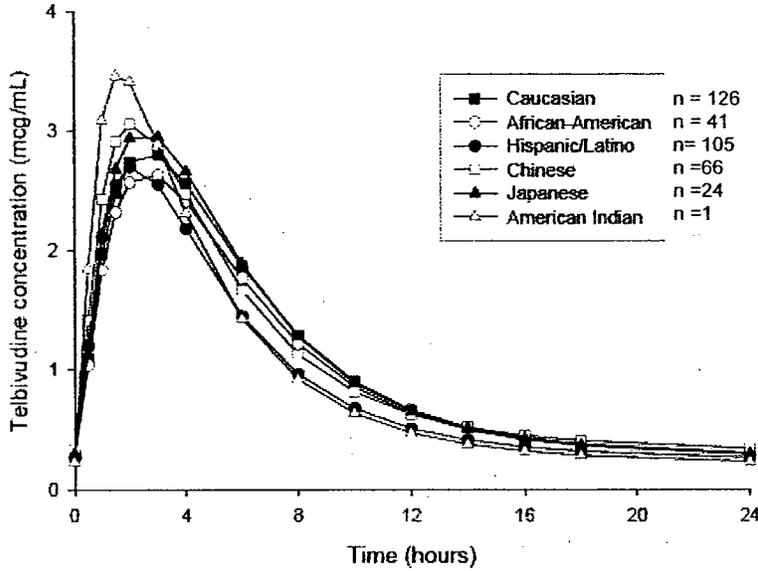
In the population PK analysis, volume of distribution (V) was found to be proportional to patient weight. Over the body weight range observed in these studies (43 kg – 110 kg), V ranged from 19.26 L to 49.27 L, with heavier patients exhibiting a larger central volume of distribution compared to lighter subjects. The overall impact of this change in V<sub>2</sub> is evident in the telbivudine concentration time profiles (Figure 2.3.1c), depicted by an increase in C<sub>max</sub>. The C<sub>max</sub> for patients with BW of 43 kg and normal CLCR are higher as compared to patients with higher BW, however, this C<sub>max</sub> value is lower than the C<sub>max</sub> value obtained after 800 mg QD in patients (5.46  $\mu\text{g/mL}$ ), and thus giving 600 mg QD to patients with lower BW should be safe. The lower C<sub>max</sub> and similar AUC for heavy weight subjects are not expected to result in any clinical significant difference in efficacy, because the C<sub>max</sub> value is similar to the C<sub>max</sub> obtained at 400 mg QD (Study NV-02B-001).

Figure 2.3.1c Simulated telbivudine steady-state concentration time profiles for subjects with normal creatinine clearance and varying body weights receiving 600 mg/day



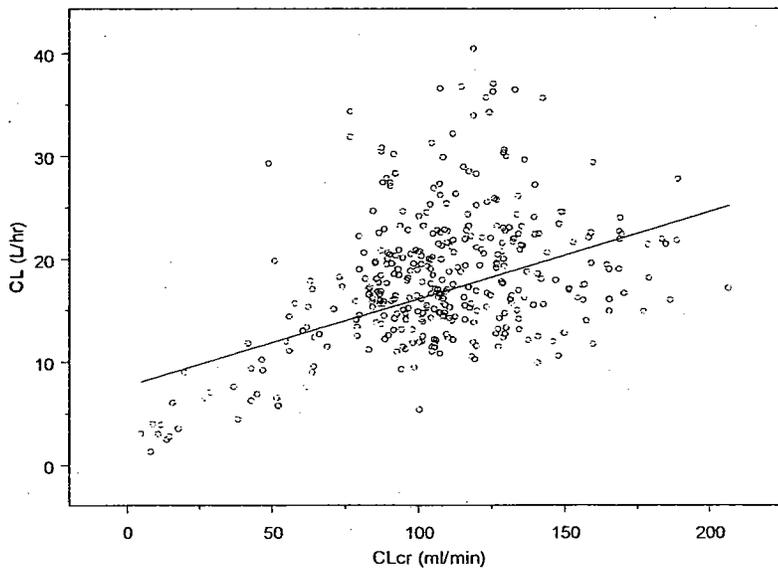
In the population PK analysis, telbivudine steady-state pharmacokinetics were predicted for Caucasian, African American, and Asian subjects. As shown in Figure 2.3.1d, no clinically significant difference was expected from different races. Therefore no dosing adjustment is required for different races.

Figure 2.3.1d Predicted steady-state concentration-time profiles by race for subjects with median body weight (71 kg) and CLCR  $\geq$  50 mL/min receiving telbivudine 600 mg/day



Population PK analysis indicated that telbivudine clearance decreases as renal function decreases (Figure 2.3.1e).

Figure 2.3.1e The Effect of CLcr on telbivudine CL



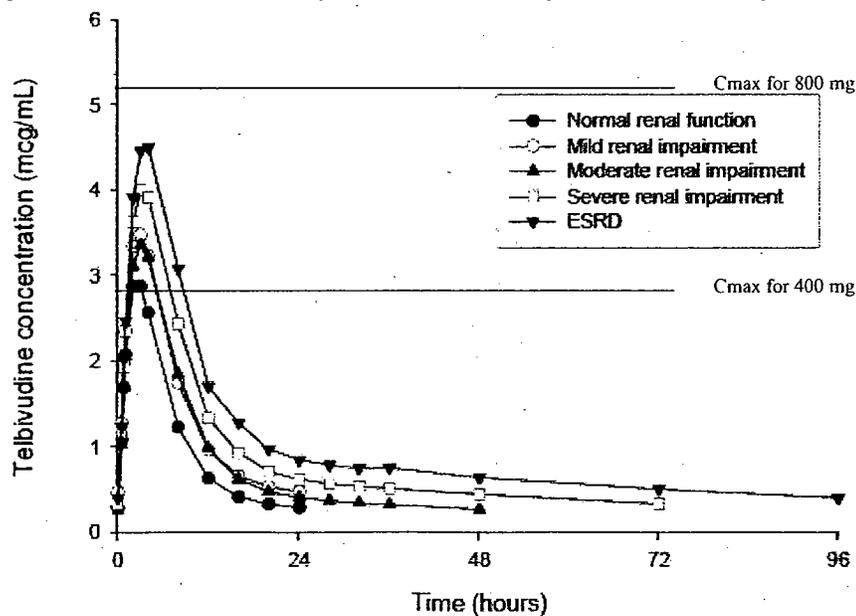
Simulations were performed to assess the effects of varying degrees of renal impairment on the pharmacokinetics of telbivudine using the final model parameter estimates from the population PK analysis and the demographic data from the renal impairment study (Study NV-02B-006). The following simulations were performed: 600 mg daily for subjects with normal renal function and mild renal impairment, 600 mg administered every 48 hours for subjects with moderate renal impairment, 600 mg administered every 72 hours or every 96 hours for subjects with severe renal impairment, and 600 mg administered every 96 hours or every 168 hours for subjects with end-stage renal disease (ESRD, telbivudine administered after hemodialysis). A summary of the parameters and telbivudine concentration time profiles from these simulations is presented in Table 2.3.1a and Figure 2.3.1f.

Table 2.3.1a Estimates of steady-state AUC, Cmax, and Cmin for patients with varying degrees of renal impairment receiving telbivudine 600 mg according to various dosage interval adjustments

Renal Function	$\tau$ (hours)	Cmin ( $\mu\text{g/mL}$ )	Cmax ( $\mu\text{g/mL}$ )	AUC $_{\tau}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	AUC ratio (AUC $_{\tau}$ )
0	24	0.288 $\pm$ 0.072	2.898 $\pm$ 0.386	24.824 $\pm$ 4.131	1.03 $\pm$ 0.17
1	24	0.473 $\pm$ 0.051	3.476 $\pm$ 0.244	33.438 $\pm$ 2.223	1.39 $\pm$ 0.09
2	48	0.288 $\pm$ 0.032	3.370 $\pm$ 0.268	40.434 $\pm$ 3.899	0.84 $\pm$ 0.08
3	72	0.330 $\pm$ 0.123	4.030 $\pm$ 0.708	63.852 $\pm$ 15.190	0.89 $\pm$ 0.21
3	96	0.210 $\pm$ 0.079	3.915 $\pm$ 0.678	63.827 $\pm$ 15.183	0.66 $\pm$ 0.18
4	96	0.400 $\pm$ 0.159	4.508 $\pm$ 0.706	93.868 $\pm$ 21.960	0.98 $\pm$ 0.23
4	168	0.152 $\pm$ 0.071	4.270 $\pm$ 0.626	93.808 $\pm$ 21.940	0.56 $\pm$ 0.13

Renal category: 0=normal renal function, 1=mild renal impairment, 2=moderate renal impairment, 3=severe renal impairment, 4=ESRD.

Figure 2.3.1f Simulated steady-state concentrations following the administration of telbivudine 600 mg every 24 hours in subjects with normal renal function or mild renal impairment, every 48 hours subjects with moderate renal impairment, every 72 hours for subjects with severe renal impairment, and every 96 hours for subjects with ESRD





Telbivudine is not a substrate of CYP enzymes. No metabolites of telbivudine were detected in plasma, urine, or feces following administration of [<sup>14</sup>C]-telbivudine in humans, indicating that CYP450 does not play a role in the metabolic clearance of telbivudine.

#### *2.4.2.3. Is the drug an inhibitor and/or inducer of CYP enzymes?*

An *in vitro* study was conducted to evaluate the potential for telbivudine to inhibit CYP catalytic activity, specifically CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (study 02-CP-005). The following probe substrates were utilized: phenacetin (1A2), diclofenac (2C9), *S*-mephenytoin (2C19), bufuralol (2D6), *p*-nitrophenol (2E1), and midazolam (3A4). Telbivudine concentrations tested ranged from 0.4 to 40 µg/mL. Estimated IC<sub>50</sub> values for L-Thymidine are >40 µg/mL, the highest test article concentration used. The data indicate that *in vitro* L-dT is not an inhibitor of cytochrome P450 CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Therefore, *in vivo* interaction studies of telbivudine and concomitant medications eliminated by these pathways are not needed.

Animal study shows that telbivudine is not an inducer of CYP enzymes; however, no *in vitro* study in human hepatocytes or *in vivo* study in human has been conducted to show telbivudine is not an inducer of CYP enzymes.

#### *2.4.2.4. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

An *in vitro* transport experiment was conducted to evaluate telbivudine as a substrate of human P-glycoprotein (P-gp) using Caco-2 cells. However, positive control, digoxin was not included in the study. In addition, an *in vivo* drug-drug interaction study was conducted with a P-gp inhibitor, cyclosporine. The study shows that cyclosporine does not interact with telbivudine, indicating that telbivudine is not a P-gp substrate. The potential for telbivudine to inhibit P-gp was not evaluated.

#### *2.4.2.5. Are there other metabolic/transporter pathways that may be important?*

Telbivudine is excreted mainly by passive diffusion so the potential for interactions between telbivudine and other drugs eliminated by renal excretion is low. However, because telbivudine is eliminated primarily by renal excretion, co-administration of telbivudine with drugs that alter renal function may alter plasma concentrations of telbivudine. Clinical studies evaluating the potential for pharmacokinetic interaction involving drugs eliminated via active tubular secretion (specifically lamivudine, adefovir dipivoxil, cyclosporine and pegylated interferon-alfa 2a) were conducted in the telbivudine development program. There were no clinically significant drug interactions. See section 2.4.2.7 for further description of drug interaction study results.

#### *2.4.2.6. What other co-medications are likely to be administered to the target patient population?*

In the treatment of HBV infection, combination therapy with two drugs in patient populations who fail monotherapy and/or in treatment-naïve patients is a potentially viable option for therapy, specifically with nucleoside and nucleotide analogs.

In addition, in patient populations co-infected with HBV and HIV-1, multiple drug regimens are anticipated. Therefore, the focus of the drug-drug interaction evaluation for

telbivudine included antivirals indicated for the treatment of HBV, as well as HIV-1, and that have demonstrated potential for altering renal function.

*2.4.2.7. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

Drug-drug interaction studies show that lamivudine, adefovir dipivoxil, cyclosporine and pegylated interferon-alfa 2a do not alter telbivudine pharmacokinetics (Figure 2.4.1a). Figure 2.4.1b shows that telbivudine does not alter the pharmacokinetics of lamivudine, adefovir dipivoxil, or cyclosporine. No definitive conclusion could be drawn regarding the effects of telbivudine on the pharmacokinetics of pegylated interferon-alfa 2a due to the high inter-individual variability of pegylated interferon-alfa 2a concentrations.

At concentrations up to 12 times that in humans, telbivudine did not inhibit *in vitro* metabolism mediated by any of the following human hepatic microsomal cytochrome P450 (CYP) isoenzymes known to be involved in human medicinal product metabolism: 1A2, 2C9, 2C19, 2D26, 2E1, and 3A4. Based on the above results and the known elimination pathway of telbivudine, the potential for CYP450-mediated interactions involving telbivudine with other medicinal products is low.

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Figure 2.4.1a The effects of other coadministered drugs on telbivudine exposure

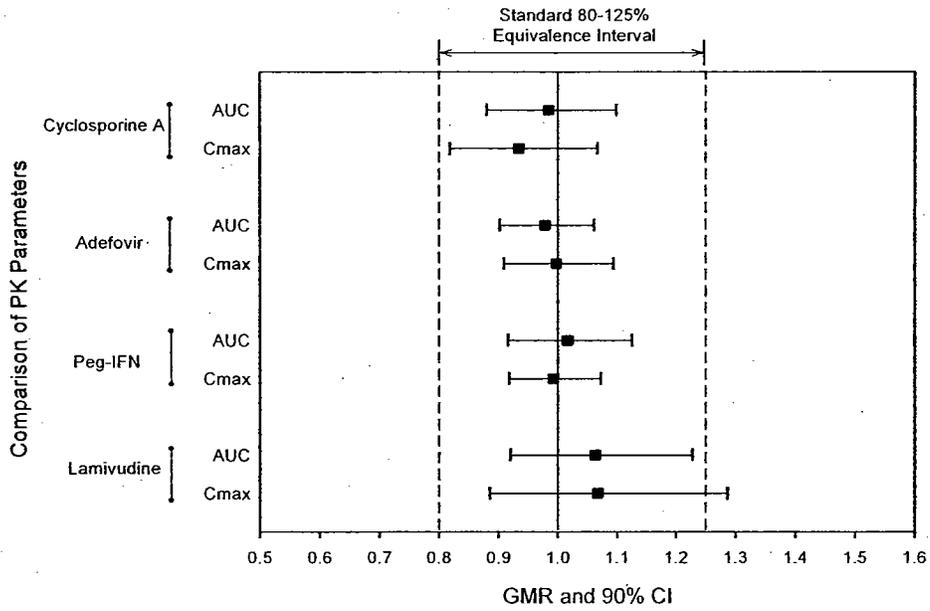
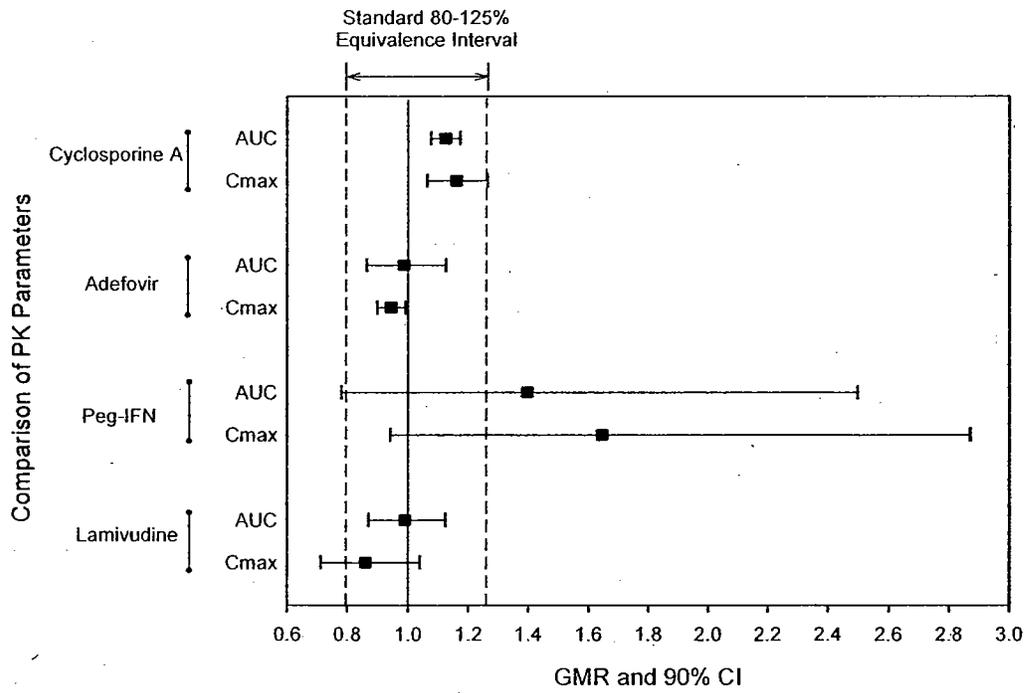


Figure 2.4.1b The effects of LdT on exposure of other coadministered drugs



## 2.5 General Biopharmaceutics

### 2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Telbivudine is highly soluble in water (20 mg/mL) and in the pH range of 4.0 to 9.0. The permeability study using Caco-2 indicated telbivudine is medium permeable (10 -30 nm/sec).

### 2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

A pivotal BE study was conducted to compare the relative bioavailability of the proposed to-be-marketed formulation (Treatment B, test, 600 mg tablets) to the formulation used in the clinical trials (Treatment A, reference, 200 mg tablets). The study shows that the 90% CI for the geometric mean ratios for C<sub>max</sub> and AUC were within the range of 80% - 125% for bioequivalence (Table 2.5.2a). Therefore, the proposed to-be-marketed formulation is bioequivalent to the formulation used in the clinical trials.

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Table 2.5.2a Statistical comparison between the proposed to-be-marketed formulation (Treatment B, test) to the formulation used in the clinical trials (Treatment A, reference)

Parameter	Treatment	Adjusted Geometric mean	Ratio of Adjusted Geometric mean (95% CI)
Cmax (ng/mL)	Test	3118	106.8 (98.21-116.04)
	Reference	2921	
AUC (0-t) (ng.h/mL)	Test	28739	106.1 (99.16-113.59)
	Reference	27065	
AUC (0-inf) (ng.h/mL)	Test	30363	105.9 (99.06-113.16)
	Reference	28681	

The report from Division of Scientific Investigations (DSI) indicates that the clinical and analytical data from this pivotal BE study are acceptable.

**2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

The effect of food on the pharmacokinetics of telbivudine administered as a single dose was studied under fasted condition in healthy subjects. Telbivudine absorption and exposure were unaffected when a single 600 mg dose was administered with a high-fat (54.6 g), a high-calorie (950 kcal) meal. Pharmacokinetic parameters of telbivudine including Cmax, AUC (0-t and 0-∞) and T1/2 were comparable between the fed and fasted treatments. The 90% confidence intervals all were within the critical range of 80.0 -125.0 % for bioequivalence (Table 2.5.3a). Telbivudine may be taken with or without food.

Table 2.5.3a Summary of the pharmacokinetic and statistical results of plasma telbivudine for fasted and fed treatments

PK Parameters	Fasting, reference Arithmetic mean (SD)	Fed, test Arithmetic mean (SD)	Geometric mean ratio	90% CI
Cmax (ng/mL)	2706 (704)	2798 (686)	103.8	96.4 - 111.9
AUC0-t (ng/mL×h)	19639 (5417)	20766 (4747)	107.2	98.0 - 117.2
AUC0-∞ (ng/mL×h)	21818 (5487)	22962 (5016)	106.4	98.6 - 114.8
Tmax (hr)*	3.0 (1.0 - 6.0)	3.0 (2.0 - 4.0)		
T1/2 (hr)	17.3 (6.0)	16.8 (5.9)	95.9	86.3 - 106.5

\* Median (range) instead of mean (SD).

**2.5.4. How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?**

The applicant and FDA agree on the following method and specification:

Apparatus: Paddle, USP dissolution apparatus 2

Rotation: 50 rpm

Temperature: 37 ± 0.5°C

Medium: 900 mL of 0.1 N HCl  
Sampling Time: 15, 30 and 45 minutes  
Q = — in 30 minutes.

Comparative dissolution testing was conducted in three media: 0.1 N HCl, pH 4.5 phosphate buffer, and pH 6.8 phosphate buffer. The tested batches (Table 2.5.4a) are those used in the pivotal bioequivalence study.

Table 2.5.4a Batches of 200 mg tablets and 600 mg film-coated tablets used in the pivotal bioequivalence study

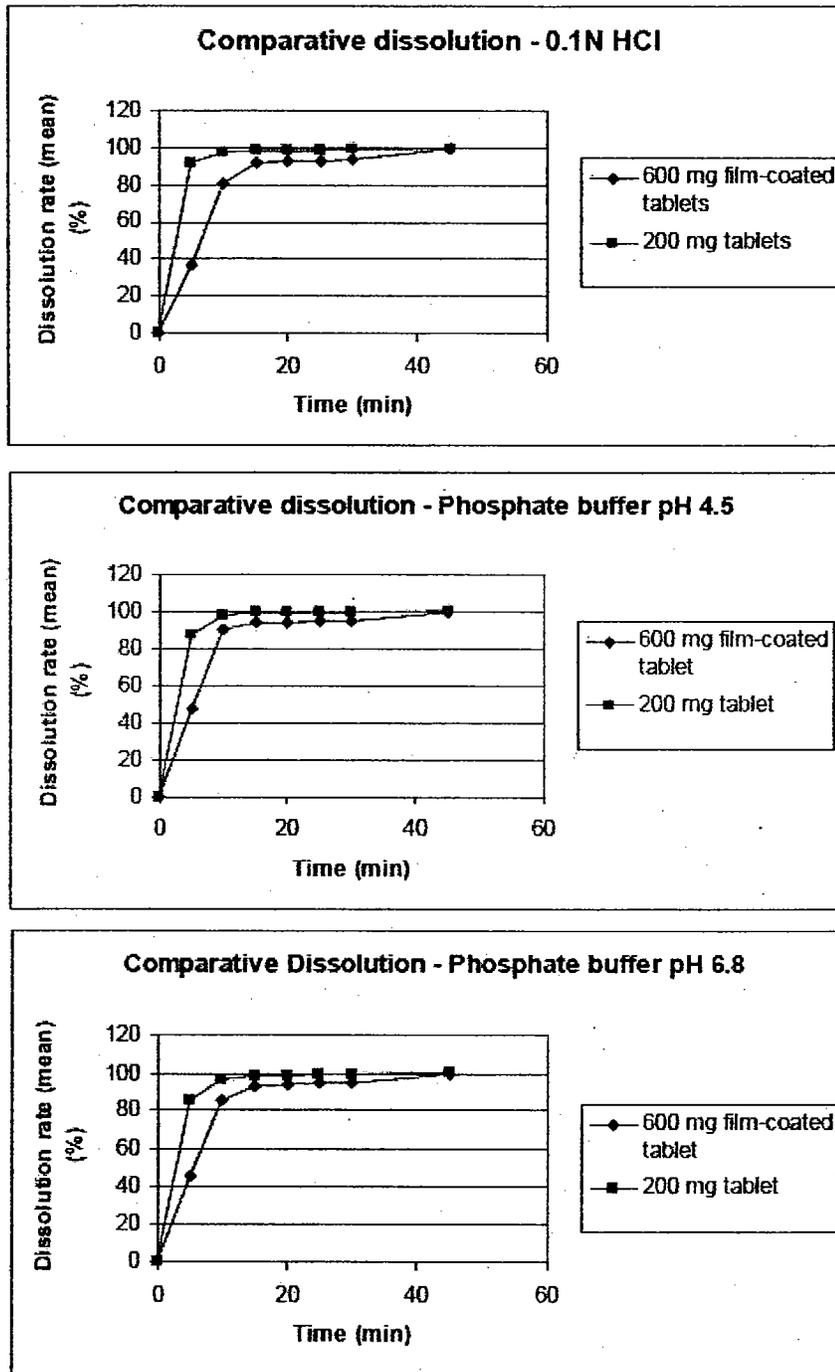
Batch no.	Strength / dosage form	Type	Use	Formulation code <sup>1</sup>
X378KA	600 mg film-coated tablet	Production batch	Process validation Bioequivalence	6001474.004
X247 0804	200 mg tablet	Production batch	Bioequivalence Clinical batch	6001198.002

<sup>1</sup> Novartis internal code

Dissolution data are provided in graphic form in Figure 2.5.4a and in Tables 2.5.4b, 2.5.4c and 2.5.4d.

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Figure 2.5.4a Comparative dissolution profile of telbivudine 200 mg tablets and telbivudine 600 mg film-coated tablets





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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

## 2.6 Analytical Section

### 2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What bioanalytical methods are used to assess concentrations?

Telbivudine concentrations in human plasma and urine samples were determined by validated liquid chromatographic methods using LC/MS/MS. The assay is acceptable. In the first human study (NV-02B-001), an HPLC technique with UV detection was first applied to samples from dose cohorts of 25 to 400 mg. This methodology has a limited sensitivity (LOQ-  ) and has proved to be less adequate for the lower dose cohorts (25 and 50 mg). (See individual studies for details).

### 2.6.2 Which metabolites have been selected for analysis and why?

Telbivudine alone was selected for analysis because no metabolites were detected in plasma, urine, or feces after administration of a single oral dose of 600 mg [<sup>14</sup>C]-telbivudine.

### 2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Because protein binding of telbivudine is low (approximately 3.3%) and independent of concentration, total telbivudine concentrations were measured in the clinical pharmacology studies.

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### **3. DETAILED LABELING RECOMMENDATIONS**

- The CLINICAL PHARMACOLOGY/Absorption and Bioavailability Section needs to be rewritten to reflect the following changes:
  - Remove dose-proportionality information
  - Change PK information from single dose to steady-state.
- Add specific meal type in the CLINICAL PHARMACOLOGY/Effects of Food on Oral Absorption.
- The Drug Interactions section under CLINICAL PHARMACOLOGY and PRECAUTION are rewritten to clarify the direction of drug-drug interaction, and to remove information regarding CYP induction potential based on animal data.
- Hemodialysis information is added to OVERDOSAGE section for alternative management of overdose.

### **4. APPENDICES**

#### **4.1 Proposed Package Insert**

The following shows the Clinical Pharmacology section in the final label.

#### **CLINICAL PHARMACOLOGY**



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           § 552(b)(4) Trade Secret / Confidential

           § 552(b)(5) Deliberative Process

✓           § 552(b)(5) Draft Labeling

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Jenny H. Zheng  
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BIOPHARMACEUTICS

Kellie Reynolds  
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