

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-011**

**CHEMISTRY REVIEW(S)**



**NDA 22-011**

**TYZEKA<sup>TM</sup>**  
**(Telbivudine)**  
**Tablets**

**600 mg**

**Idenix Pharmaceutical Inc.**

**Ko-Yu Lo, Ph.D.**  
**Branch IV**  
**Division of Pre-Marketing Assessment 2**  
**Office of New Drug Quality Assessment**

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# Chemistry Review Data Sheet

1. NDA or ANDA 022-011
2. REVIEW #: 1
3. REVIEW DATE: 10/24/2006
4. REVIEWER: Ko-Yu Lo
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

30/DEC/2005

Amendment BC

03/MAR/2006

Amendment BC

16/OCT/2006

7. NAME & ADDRESS OF APPLICANT:

Name	Idenix Pharmaceuticals, Inc.
Address	60 Hampshire Street, Cambridge, MA 02139 .
Representative	David Hallinan, Ph.D.
Telephone	617-995-9800

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Telbivudine
- c) Code Name/# (ONDC only): LdT
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 600 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  X  Rx   OTC

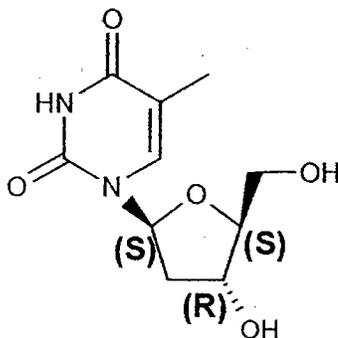
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN	Telbivudine
Chemical Name	1-((2S,4R,5S)-4-Hydroxy-5-hydroxymethyltetrahydrofuran-2-yl)-5-methyl-1H-pyrimidine-2,4-dione
CAS Name	1-(2-Deoxy-β-L-erythro-pentofuranosyl)-5-methyl-2,4(1H,3R)pyrimidinedione
CAS Reg. No.	3424-98-4
Other Names	1-(2-Deoxy-β-L-ribofuranosyl)-5-methyluracil, 1-(2-Deoxy-β-L-ribofuranosyl)thymine, β-L-Thymidine, 2'-Deoxy-β-L-thymidine, L-Thymidine
Molecular Formula	C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub>
Molecular Weight	242.23
Structure Formula	Telbivudine, which presents 3 chiral centers, is the pure isomer with absolute configuration 2S, 4R and 5S.





# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TY PE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
-	III	██████████		3	Adequate		
-	III	██████████			Adequate		
-	III	██████████		3	Adequate		
-	III	██████████		3	Adequate		
-	III	██████████		3	Adequate		
-	IV	██████████		4	Adequate		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,459	Telbivudine Tablets and ██████████

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

EES	Acceptable	3/17/2006	HFD-322
Pharm/Tox	Acceptable	10/12/2006	Ita Yen
Biopharm	Dissolution Specification Acceptable	10/12/2006	Jenny H Zhang & Ko-Yu Lo
LNC	N/A		
Methods Validation	Not need		
OPDRA	Acceptable		
EA	Exclusion Acceptable	10/12/2006	Ko-Yu Lo
Microbiology	N/A		

### OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:

**Appears This Way  
On Original**



# The Chemistry Review for NDA 22-011

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval.

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

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance, telbivudine ( $\beta$ -L-thymidine, LdT) is a synthetic thymidine nucleoside analogue with activity against hepatitis B virus (HBV). Telbivudine is a chiral compound with the 2S, 4R and 5S absolute configuration and is the unmodified  $\beta$ -L enantiomer of the naturally occurring nucleoside, thymidine.

Telbivudine is

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commercial manufacturing process as well as controls for starting materials, reagents, process intermediate, and the new drug substance is acceptable.

The structure of LdT has been established by elemental analysis, UV/VIS, FTIR, ESI/MS,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR. Possible impurities (related substances) introduced during synthesis or degradation products formed during synthesis and /or storage have been studied extensively. A comparison of the nonclinical, clinical and launch batches shows very low amount of related substances (<0.05% reporting threshold) and low amounts of residual solvents (1/3 to 1/10 of the ICH Q3C limits). Only

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A reference standard has been prepared.



## CHEMISTRY REVIEW

### Executive Summary Section

\_\_\_\_\_

\_\_\_\_\_

on ICH guidance Q3B(R) instead of existing data (<0.1%). The DP specification is established based on data (release and stability) from 3 registration stability batches and release data from 3 process validation batches.

Stability of the drug product has been evaluated on 3 stability batches \_\_\_\_\_ at long term conditions (25°C/60%RH, and 30°C/70%RH) for 12 months, accelerated conditions (40°C/75%RH) for 6 months, and at -20°C, 5°C and 50°C/ambient RH and under light irradiation. No significant change was observed for all parameters tested. No degradation products were detected above the reporting limits. Statistical analysis (ANOVA) of the stability data has been performed. A \_\_\_\_\_ shelf-life was predicted using linear regression and a 95% 1-side lower prediction interval approach.

#### **B. Description of How the Drug Product is Intended to be Used**

TYZEKA (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.

The recommended dose of TYZEKA Tablets is 600 mg once daily, taken orally, with or without food.

TYZEKA Tablets are packaged in \_\_\_\_\_ bottles as 30 counts per bottle. The bottles are stored at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F).

A 24 months expiration dating period is approved based on (i) the product is stable at 25°C/60%RH and 30°C/70%RH for 12 months and 40°C/75%RH for 6 months, (ii) no degradation products were detected at all tested conditions and (iii) \_\_\_\_\_; shelf-life was predicted using linear regression and a 95% 1-side lower prediction interval approach

#### **C. Basis for Approvability or Not-Approval Recommendation**

After pre-approval inspection, all manufacturing and testing facilities were found acceptable.

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for the product of TYZEKA™ Tablets, 600 mg.

**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: 10/12/06  
ChemistryTeamLeaderName/Date  
ProjectManagerName/Date

**C. CC Block**



46 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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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.**  
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/s/

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Ko-yu Lo  
10/24/2006 03:23:02 PM  
CHEMIST

Rapti Madurawe  
10/24/2006 04:26:29 PM  
CHEMIST  
(for Norman Schmuff)