APPLICATION NUMBER:
22-011

CHEMISTRY REVIEW(S)
NDA 22-011

TYZEKA™
(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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1. NDA or ANDA 022-011

2. REVIEW #: 1

3. REVIEW DATE: 10/24/2006

4. REVIEWER: Ko-Yu Lo

5. PREVIOUS DOCUMENTS:

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6. SUBMISSION(S) BEING REVIEWED:

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7. NAME & ADDRESS OF APPLICANT:

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<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Address</td>
<td>60 Hampshire Street, Cambridge, MA 02139</td>
</tr>
<tr>
<td>Representative</td>
<td>David Hallinan, Ph.D.</td>
</tr>
<tr>
<td>Telephone</td>
<td>617-995-9800</td>
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</table>

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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_{10}H_{14}N_{2}O_{4}
   Molecular Weight: 242.23
   Structure Formula: Telbivudine, which presents 3 chiral centers, is the pure isomer with absolute configuration 2S, 4R and 5S.
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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1 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")

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

B. Other Documents:

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18. STATUS:

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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 (β-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 β-L enantiomer of the naturally occurring nucleoside, thymidine.

Telbivudine is a 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, $^1$H NMR and $^{13}$CNMR. 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

A reference standard has been prepared.

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LdT drug substance is a white to slightly yellowish powder. Specification for the DS includes appearance, particle size, identification, assay, API content, impurities (related substances, enantiomer, and anomer), residual solvents, clarity and color of solution, and microbial limit tests. Acceptance criteria (AC) of 0.1% for related substances are proposed based on ICH guidance Q3A(R) instead of existing data (<0.05% of reporting threshold). Similarly, the ACs for residual solvents are proposed based on ICH guidance Q3C. The FDA finds the applicant’s proposal acceptable based on risk assessment: (i) an impurity level of 0.1% is in accord with the ICH Q3A(R) guidance and (ii) higher levels of related substances at <1% have been qualified in the toxicological studies. The DS specification is established based on the release data from nonclinical, clinical and launch batches and the stability data from 3 registration stability batches.

Stability of the DS has been evaluated on 3 registration batches at long-term conditions (25°C/60%RH), intermediate conditions (30°C/70%RH) for and accelerated conditions (40°C/75%RH) for The existing data support a

The drug product, TYZEKA™ Tablets, 600 mg is a white to slightly yellowish, ovaloid, slightly curved film-coated tablet. Pharmaceutical development studies have been performed. Rationale for formulation changes, excipient selection and optimization were discussed. A 200 mg tablet formulation was used in the Phase III clinical trials. The selection of the 600 mg film-coated tablets as the commercial formulation was based on clinical need for a high drug load, its bioequivalent, comparable disintegration and dissolution to the 200 mg tablets, and its high robustness in terms of process parameter variation.

TYZEKA film-coated tablet is manufactured by Novatis Pharma Stein AG via an
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
   Chemistry/TeamLeaderName/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

Withheld Track Number: Chemistry
This is a representation of an electronic record that was signed electronica and this page is the manifestation of the electronic signature.

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

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