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APPLICATION NUMBER:

22-154

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 25, 2009
From	Linda L. Lewis, M.D. Medical Officer Team Leader DAVP/OAP/CDER/DAVP
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-154/000
Applicant	Novartis Pharmaceuticals
Date of Submission **Date of Resubmission**	December 21, 2007 February 27, 2009
PDUFA Goal Date	April 28, 2009
Proprietary Name / Established (USAN) names	Tyzeka™ / telbivudine
Dosage forms / Strength	Oral solution / 100 mg/5 mL
Proposed Indication(s)	1. Treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease
Recommended:	***Approval, with labeling as amended***

1. Introduction

Tyzeka™ (telbivudine) 600 mg tablets were approved for the treatment of chronic hepatitis B virus (HBV) infection in adult patients with compensated liver disease on October 25, 2006, following review of NDA 22-011. The current application for Tyzeka™ Oral Solution was submitted on December 21, 2007, by Idenix Pharmaceuticals on behalf of Novartis Pharmaceuticals after ownership of the drug was transferred to Novartis. The original submission of NDA 22-154 contained CMC information for the new oral solution formulation and proposed new dosing recommendations for patients with varying degrees of renal impairment. The oral solution was determined to be bioequivalent to the tablets at the time of the original Tyzeka tablet approval.

The dosing recommendations for renal impairment were reviewed and the Clinical Pharmacology Reviewer did not agree with the recommendation for patients with end

stage renal disease requiring dialysis (ESRD). In addition, the applicant proposed to

[redacted] For these reasons, a Complete Response (CR) letter was issued on October 21, 2008. This submission represents the applicant's resubmission following the CR and addresses all issues described in the CR letter. It does not contain any new clinical data. For additional information regarding the original NDA 22-154 submission, please refer to my CDTL memo dated October 17, 2008.

b(4)

2. Background

Tyzeka (telbivudine) is a synthetic thymidine nucleoside analogue that acts as a selective inhibitor of HBV DNA polymerase. It was demonstrated to provide treatment effects similar to those of lamivudine in a single, large, randomized, double-blind, comparative trial (NV-02B-007, the GLOBE study) enrolling patients with chronic HBV infection who were both e antigen positive (HBeAg+) and e antigen negative (HBeAg-). Treatment with Tyzeka 600 mg once daily was shown to result in decreased HBV DNA levels, normalization of serum ALT, and loss of HBeAg (in HBeAg+ subgroup) over 52 weeks of dosing. Improvement in liver histology was also similar between the two treatment arms as shown in paired baseline and Week 52 liver biopsies.

The original NDA 22-011 also provided results of two studies pertinent to the review of NDA 22-154, a clinical pharmacology study in patients with renal impairment (NV-02B-006) and a bioequivalence study comparing the approved 600 mg tablet to the proposed oral solution (NV-02B-025). On the basis of Study NV-02B-006, dose recommendations for the Tyzeka tablets given at increasing intervals for increasing renal impairment (ie. decreasing creatinine clearance) were included in the original product label.

As part of a recent efficacy supplement for NDA 22-011, a review of post-marketing safety data for Tyzeka and the applicant's reports of serious adverse events in an ongoing clinical trial (CLDT600A2406) led to concern regarding a new safety signal for peripheral neuropathy. Consequently, the Review Team recommended that the applicant convert the current Patient Package Insert for Tyzeka to a Medication Guide and also propose a Risk Evaluation and Mitigation Strategy (REMS). The tablets and oral solution formulations will share a single package insert and Medication Guide. The REMS will also apply to NDA 22-154 and a REMS modified to include this NDA has been submitted.

As noted, no new data are presented in the current re-submission. The applicant has

b(4)

[redacted]

3. CMC/Device

The oral solution formulation of Tyzeka, manufactured by Novartis Pharma Stein AG, is a clear to pale yellow solution containing 20 mg/mL of LdT. The inactive ingredients include: citric acid anhydrous, benzoic acid, Passion fruit flavor, sodium saccharin, sodium hydroxide, and water. A 30 mL volume of the oral solution provides the standard adult dose of 600 mg. The oral solution will be provided in 300 mL bottles with child-resistant closure and an embossed dosing cup. Specifics of the manufacturing process, in-process controls, drug product specifications, and stability testing were reviewed and found to be acceptable by Dr. Andrew Yu at the time of the initial submission. In addition, the applicant's current proposal to dose patients with 30, 20, or 10 mL as measured by the dosing cup [redacted] b(4)
[redacted] are acceptable from a CMC perspective. The applicant provided data to support that [redacted] were adequately tested and that construction and performance of the devices is acceptable.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology data submitted with this NDA.

5. Clinical Pharmacology/Biopharmaceutics

Two studies reviewed in the original NDA 22-011 were relevant to the review of NDA 22-154. Results from Study NV-02B-025 demonstrated that the approved 600 mg tablet was bioequivalent to the new oral solution. Results of Study NV-02B-006, in which Tyzeka tablets were administered to subjects with varying levels of renal impairment, provided data for dose recommendations for Tyzeka tablets given at increasing intervals for increasing renal impairment. The initial NDA 22-154 submission used results of these studies and PK simulations to make dosing recommendations for Tyzeka oral solution given on a daily basis. The proposed dosing for patients with renal impairment using either tablets or oral solution is shown below:

Table 1: Dose Adjustment of Telbivudine in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Proposed Oral Solution Dose	Approved Tablet Dose
≥ 50	30 mL (600 mg) every 24 hrs	600 mg every 24 hrs
30–49	20 mL (400 mg) every 24 hrs	1 tablet every 48 hrs
<30 (not requiring dialysis)	10 mL (200 mg) every 24 hrs	1 tablet every 72 hrs
ESRD requiring dialysis	[redacted]	1 tablet every 96 hrs

b(4)

In the CR letter, additional information was requested in order to verify the dose recommendation for patients with end-stage renal disease requiring dialysis. FDA Clinical Pharmacology Reviewer, Dr. Jenny Zheng, disagreed with the applicant's [redacted]

b(4)

. For a complete review of the proposed dosing in patients with renal impairment, please refer to the Clinical Pharmacology Review submitted by Dr. Zheng.

6. Clinical Microbiology

No new virology data were submitted with this NDA.

7. Clinical/Statistical- Efficacy

No new efficacy data were submitted with this NDA.

8. Safety

No new safety data were submitted with this NDA.

The current submission contains instructions for patients describing how to administer doses of Tyzeka oral solution for adult patients who may require doses of 30, 20, 10, b(4) once daily. The instructions for use of the dosing cup to measure 30, 20, or 10 mL are acceptable. However, the applicant proposes This process involves b(4) Both the Clinical Review Team and the review team from the Division of Medication Error Prevention (DMEPA) considered this proposal to be too complicated, prone to errors in measuring, and wasteful of drug. b(4)

In addition, the DMEPA review identified that the proposed dosing cup has multiple demarcations, including some that do not correspond to Tyzeka dose recommendations, making it difficult to read. They recommended that a new dosing device be designed that included only demarcations for recommended doses. For more details on their recommendations, please refer to the DMEPA Safety Review performed by Denise Baugh.

The Division of Risk Management (DRISK) was consulted to review the proposed REMS and Medication Guide. The REMS for Tyzeka oral solution is unchanged from

the one submitted to NDA 22-011 and previously reviewed except for the addition of NDA 22-154. The DRISK review concluded that the REMS and Medication Guide were acceptable. Additional comments from DRISK were forwarded to the applicant.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held regarding this supplement.

10. Pediatrics

This NDA seeks approval of an oral solution formulation of Tyzeka but the initial proposed use for this formulation is to provide optimal dosing in adult patients with renal impairment or to provide dosing for adults who can not swallow tablets. Since this NDA seeks approval for a new dosage form for Tyzeka, it triggers pediatric postmarketing requirements under the Pediatric Research Equity Act (PREA) and the pediatric development plan was reviewed by the FDA's Pediatric Review Committee (PeRC).

The pediatric development plan includes 3 clinical trials in patients from 2 to < 18 years of age:

- [redacted]
- [redacted]
- [redacted]

b(4)

The pediatric plan and the applicant's request for deferral of pediatric studies were submitted to the PeRC on April 8, 2009, and were approved. Studies in patients 2 to < 18 years of age are deferred since the pediatric studies are not yet complete but the product is ready for approval in adults. Evaluation of pediatric patients < 2 years of age is deferred because additional safety and efficacy data are needed before beginning study in this age group. Treatment is rarely initiated in the first two years of life in patients with chronic HBV infection and this age group may be waived in the future if this continues to be the consensus opinion at the time the PK, safety, and efficacy data are available from older pediatric patients.

The following postmarketing studies are required under the terms of PREA as re-authorized in FDAAA of 2007.

1. Deferred pediatric study/substudy for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from 2 to <18 years of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from 2 to < 18 years of age to support dose-selection for the efficacy and safety assessment.

Protocol Submission: completed
Study Start Date: March, 2009
Final Report Submission: September, 2010

2. Deferred pediatric study for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from 2 through < 18 years of age. Using doses selected based on the substudy listed under item 1 above, conduct a pediatric safety and efficacy study of telbivudine with efficacy based on virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.

   Protocol Submission: March, 2010
   Study Start Date: September, 2010
   Final Report Submission: September, 2013

3. We are deferring submission of your pediatric PK dose selection and efficacy studies in patients from birth to < 2 years of age because these pediatric studies should be delayed until additional safety or effectiveness data have been collected. We anticipate waiting for completion and review of studies in pediatric patients 2 to < 18 years age before determining whether it is appropriate to study telbivudine for HBV in the birth to < 2 years age group. According to experts in pediatric HBV disease (pediatric hepatologists), treatment is rarely initiated in the first two years of life in patients with chronic HBV infection and this group may be waived in the future if this continues to be the consensus at the time the safety data are available or if the risk/benefit assessment is not favorable based on safety data from older pediatric patients.

   Protocol Submission: January, 2013
   Study Start Date: March, 2013
   Final Report Submission: September, 2016

In addition, a Pediatric Written Request was issued December 1, 2006 (due July 1, 2010), and subsequently amended July 24, 2007, reiterating the request for data supporting dose recommendations, safety, and efficacy in pediatric patients 2 through 16 years of age.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues that need to be addressed for this supplement.

12. Labeling

The applicant proposes a single product label for both Tyzeka tablets and oral solution. The proposed labeling, as amended, includes dosing for patients with renal impairment [redacted] b(4)

13. Recommendations/Risk Benefit Assessment

I agree with the Review Team's recommendation to approve NDA 22-154 for Tyzeka oral solution for treatment of chronic hepatitis B in adults who can not swallow tablets or who require dose adjustment because of renal impairment [redacted] b(4)

In addition, the current proposed dosing cup is difficult to read and potentially prone to error and we discussed with the applicant our recommendation to redesign the dosing cup to include demarcations for all adult dosing (30, 20, 10 [redacted], without extraneous markings. The applicant has agreed to pursue the dosing cup redesign as a Postmarketing Commitment. The following Postmarketing Commitment will be included in the approval letter: b(4)

> Develop a dosing cup for distribution with Tyzeka oral solution that has clearly marked units of measure and contains only those units that correspond to dosing recommendations included in the prescribing information.
>
> sNDA submission: January, 2010

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Lewis
4/28/2009 01:00:17 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	October 17, 2008
From	Linda L. Lewis, M.D. Medical Officer Team Leader DAVP/OAP/CDER/DAVP
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-154/000
Applicant	Novartis Pharmaceuticals (submitted by Idenix Pharmaceuticals)
Date of Submission	December 21, 2007
PDUFA Goal Date	October 21, 2008
Proprietary Name / Established (USAN) names	Tyzeka™ telbivudine
Dosage forms / Strength	Oral solution/20 mg/mL
Proposed Indication(s)	1. Treatment of chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease
Recommended:	***Complete Response letter with deficiencies:*** *See body of review*

1. Introduction

Tyzeka™ (telbivudine, LdT) 600 mg tablets were approved for use in the treatment of chronic hepatitis B virus (HBV) infection in adult patients with compensated liver disease on October 25, 2006, following review of NDA 22-011. The current application for Tyzeka™ Oral Solution was submitted by Idenix Pharmaceuticals on behalf of Novartis Pharmaceuticals after ownership of the drug was transferred to Novartis. The current NDA contains CMC information for the new oral solution formulation and proposed new dosing recommendations for patients with varying degrees of renal impairment.

2. Background

LdT is a synthetic thymidine nucleoside analogue that acts as a selective inhibitor of HBV DNA polymerase. It was demonstrated to provide treatment effects similar to those of lamivudine in a single, large, randomized, double-blind, comparative trial (NV-02B-007, the GLOBE study) enrolling patients with chronic HBV infection who were both e antigen positive.(HBeAg+) and e antigen negative (HBeAg-). Treatment with LdT 600 mg once daily was shown to result in decreased HBV DNA levels, normalization of serum ALT, and loss of HBeAg (in HBeAg+ subgroup) over 52 weeks of dosing. Improvement in liver histology was also similar between the two treatment arms as shown in paired baseline and Week 52 liver biopsies.

The original NDA 22-011 also provided results of two studies pertinent to the review of NDA 22-154, a clinical pharmacology study in patients with renal impairment (NV-02B-006) and a bioequivalence study comparing the approved 600 mg tablet to the proposed oral solution (NV-02B-025). On the basis of Study NV-02B-006, dose recommendations for the Tyzeka tablets given at increasing intervals for increasing renal impairment (ie. decreasing creatinine clearance) were included in the original product label.

The only new clinical and clinical pharmacology data submitted to support NDA 22-154 was a study report for Study NV-02B-028, a study evaluating a potential drug-drug interaction between LdT and tenofovir disoproxil fumarate (TDF). However, NDA 22-154 cross-references a simultaneous efficacy supplement to NDA 22-011 (SE-001) that provides the second year of clinical safety, efficacy, and virology data for Study NV-02B-007, as well as the clinical study report for NV-02B-015. Study NV-02B-015 is a randomized, double-blind, clinical trial of LdT compared to lamivudine in Chinese patients with chronic HBV. Review of post-marketing safety data for NDA 22-011/001 and the applicant's reports of serious adverse events in an ongoing clinical trial (CLDT600A2406) have led to concern regarding a new safety signal for peripheral neuropathy. Consequently, the Review Team recommended that the applicant convert the current Patient Package Insert for Tyzeka to a Medication Guide and also propose a Risk Evaluation and Mitigration Strategy (REMS). Submission of the Medication Guide and REMS proposal will require review by additional teams and will be considered a major amendment to the NDA supplement, thus necessitating extending the review period.

Although originally submitted simultaneously, the two NDAs will require different actions as outlined in this CDTL review. This review will focus on the multi-disciplinary review issues relevant to NDA 22-154 but the final action will also incorporate the requirement for a new Medication Guide and REMS as noted for the supplement to NDA 22-011.

3. CMC/Device

The oral solution formulation of Tyzeka, manufactured by Novartis Pharma Stein AG, is a clear to pale yellow solution containing 20 mg/mL of LdT. The inactive ingredients include: citric acid anhydrous, benzoic acid, Passion fruit flavor, sodium saccharin, sodium hydroxide, and water. A 30 mL volume of the oral solution provides the standard adult dose of 600 mg. The oral solution will be provided in 300 mL bottles with child-resistant closure and an embossed dosing cup. Specifics of the manufacturing process, in-process controls, drug product specifications, and stability testing were reviewed and found to be acceptable by Dr. Andrew Yu.

On September 12, 2008, near the end of the review cycle, the applicant proposed revised dosing recommendations for patients with end-stage renal disease included in responses to earlier CMC questions. b(4)

b(4)

The sponsor provided new labeling for this dose recommendation on September 26, 2008, and notified the Review Team that b(4)

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology data submitted with this NDA.

5. Clinical Pharmacology/Biopharmaceutics

As noted above, 2 studies reviewed in the original NDA 22-011 were relevant to the review of NDA 22-154. Results from Study NV-02B-025 demonstrated that the approved 600 mg tablet was bioequivalent to the proposed oral solution. Results of Study NV-02B-006, in which Tyzeka tablets were administered to subjects with varying levels of renal impairment, allowed labeling of dose recommendations for Tyzeka tablets given at increasing intervals for increasing renal impairment. The current submission used results of these studies and PK simulations to make dosing recommendations for Tyzeka oral solution given on a daily basis. b(4)

The proposed dosing for patients with renal impairment using either tablets or oral solution is shown below:

Table 1: Dose Adjustment of Telbivudine in Patients with Renal Impairment

Creatinine Clearance (mL/min)	Proposed Oral Solution Dose	Approved Tablet Dose
≥ 50	600 mg every 24 hrs	600 mg every 24 hrs

30–49	400 mg every 24 hrs	1 tablet every 48 hrs
<30 (not requiring dialysis)	200 mg every 24 hrs	1 tablet every 72 hrs
ESRD requiring dialysis	[redacted]	1 tablet every 96 hrs

b(4)

Study NV-02B-028, a Phase 1, multiple-dose, parallel group, study evaluating the potential for drug-drug interaction between LdT and TDF was conducted in healthy volunteers. No clinically relevant interaction was identified between the two drugs.

For a complete review of the proposed dosing in patients with renal impairment and the drug interaction study, please refer to the Clinical Pharmacology Review submitted by Dr. Jenny Zheng. Additional information will be requested in order to verify the revised dose recommendation for patients with end-stage renal disease requiring dialysis.

6. Clinical Microbiology

There were no new virology data submitted with this NDA.

7. Clinical/Statistical- Efficacy

There were no new efficacy data submitted with this NDA.

8. Safety

There were no new safety data submitted with this NDA.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held regarding this supplement.

10. Pediatrics

This NDA seeks approval of an oral solution formulation of LdT but the initial proposed use for this formulation is to provide optimal dosing in adult patients with renal impairment or to provide dosing for adults who can not swallow tablets. It is anticipated that the oral solution will be useful for pediatric dosing. In the original approval for Tyzeka tablets, the following pediatric post-marketing studies were requested under the provisions of the Pediatric Research Equity Act (PREA):

1. Deferred pediatric study/substudy under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from _____ of age. This study will determine the telbivudine exposure (pharmacokinetics profile) for pediatric subjects from _____ of age to support dose-selection for the efficacy and safety assessment. b(4)

2. Deferred pediatric study under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects from birth to 16 _____ Using doses selected based on the substudy listed under item 1 above, conduct a pediatric safety and efficacy study of telbivudine with efficacy based on virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks. b(4)

These studies were deferred (no date specified) since the adult indication was ready for approval. In addition, a Pediatric Written Request was issued December 1, 2006, and subsequently amended July 24, 2007, reiterating the request for data (specified due July 1, 2010) supporting dose recommendations, safety, and efficacy in pediatric patients 2 through 16 years of age. According to experts in managing HBV in children (pediatric hepatologists), treatment is rarely initiated in the first two years of life in patients with chronic HBV infection and this age group may be waived in the future if this continues to be the consensus opinion at the time the PK, safety, and efficacy data are available from older pediatric patients.

Since this NDA seeks approval for a new dosage form for LdT, it will also trigger pediatric postmarketing requirements under PREA and the pediatric development plan must be reviewed by the FDA's Pediatric Review Committee (PeRC) in accordance with the FDA Amendments Act of 2007. At this time, the pediatric development plan has not been assessed by the PeRC and the applicant will be asked to provide a summary of their pediatric development plan at the time they submit their response to the CR letter.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues that need to be addressed for this supplement.

12. Labeling

The applicant proposes a single product label for both Tyzeka tablets and oral solution. Since this NDA is not being approved at this time, no new labeling related to the oral solution has been incorporated into the existing label.

13. Recommendations/Risk Benefit Assessment

I agree with the Review Team's recommendation not to approve this NDA at this time. Because the applicant's revised dosing recommendations for patients with end-stage renal disease arrived late in the review cycle and were not accompanied by all the information needed by the Clinical Pharmacology Reviewer, it was not possible to verify that recommendation prior to the original action date. In addition, the current proposed dosing cup is not appropriate for the new dose recommendations and a new strategy for accurate dosing will need to be proposed and reviewed. The sponsor will be sent a letter containing our Complete Response to the application noting that the NDA may be approvable in the future if the following deficiencies are addressed:

1. [redacted] b(4)

2. [redacted] b(4)

3. [redacted]

4. Please submit revised carton and/or container labels consistent with the requirements under 21 CFR 208.24(d).

5. As noted for NDA 22-011, the patient package insert must be converted to a Medication Guide and a REMS must be proposed.

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/s/

Linda Lewis
10/21/2008 03:31:45 PM
MEDICAL OFFICER