

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-011**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

022-011

NAME OF APPLICANT / NDA HOLDER

Idenix Pharmaceuticals, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

ACTIVE INGREDIENT(S)  
telbivudine

STRENGTH(S)  
600 mg.

DOSAGE FORM  
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number 6,444,652	b. Issue Date of Patent 9/3/2002	c. Expiration Date of Patent 8/10/2019
d. Name of Patent Owner Idenix Pharmaceuticals, Inc. and Centre National de la Recherche Scientifique (CNRS) Universite Montpellier (UM)  Idenix Pharmaceuticals, Inc. maintains responsibility for this submission	Address (of Patent Owner) 60 Hampshire Street	
	City/State Cambridge, MA	
	ZIP Code 02139	FAX Number (if available) 617-995-9801
	Telephone Number 617-995-9800	E-Mail Address (if available) corcoran.andrea@idenix.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)  ☞ Andrea Corcoran, Exec. V.P., Legal & Administration, Idenix Pharmaceuticals, Inc., as representative for CNRS and UM	Address (of agent or representative named in 1.e.) 60 Hampshire Street	
	City/State Cambridge, MA	
	ZIP Code 02139	FAX Number (if available) 617-995-9801
	Telephone Number 617-995-9832	E-Mail Address (if available) corcoran.andrea@idenix.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) 2, 34 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
use of telbivudine to treat hepatitis B infection in a human

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6 Declaration/Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

**Date Signed**

*Andrea Corcoran*

12-9-05

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

**Name**

Andrea Corcoran

**Address**

60 Hampshire Street

**City/State**

Cambridge, MA

**ZIP Code**

02139

**Telephone Number**

617-995-9832

**FAX Number (if available)**

617-995-9801

**E-Mail Address (if available)**

corcoran.andrea@idenix.com

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Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

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**1. GENERAL**

a. United States Patent Number

6,569,837

b. Issue Date of Patent

5/27/2003

c. Expiration Date of Patent

8/10/2019

d. Name of Patent Owner  
Idenix Pharmaceuticals, Inc. and  
Centre National de la Recherche Scientifique (CNRS)  
Universite Montpellier (UM)

Address (of Patent Owner)

60 Hampshire Street

City/State

Cambridge, MA

Idenix Pharmaceuticals, Inc. maintains responsibility  
for this submission

ZIP Code

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E-Mail Address (if available)

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e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number (as listed in the patent) 14, 29, 30, 31, 37, 38, 39 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
use of telbivudine to treat hepatitis B infection in a human

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

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**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

**Date Signed**

*Andrea Corcoran Esq. VP Gen. Counsel Hammit Kenyon*

*12-4-05*

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**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

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**City/State**  
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**1. GENERAL**

a. United States Patent Number

6,395,716

b. Issue Date of Patent

5/28/2002

c. Expiration Date of Patent

8/10/2019

d. Name of Patent Owner

Idenix Pharmaceuticals, Inc. and  
Centre National de la Recherche Scientifique (CNRS)  
Universite Montpellier (UM)

Address (of Patent Owner)

60 Hampshire Street

City/State

Cambridge, MA

Idenix Pharmaceuticals, Inc. maintains responsibility  
for this submission

ZIP Code

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

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- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
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- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

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- 2.6 Does the patent claim only an intermediate?  Yes  No
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**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
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**4. Method of Use**

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- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) 2, 17, 18, 19, 25, 26, 27 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

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Date Signed

*Andrea Corcoran Esq. VP Legal Administration*

12-9-05

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NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

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3.2 Does the patent claim only an intermediate?  Yes  No

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4.2 Patent Claim Number (as listed in the patent) 3, 4, 9 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

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*Andrea Corcoran* *12-9-05*

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Andrea Corcoran	
Address 60 Hampshire Street	City/State Cambridge, MA
ZIP Code 02139	Telephone Number 617-995-9832
FAX Number (if available) 617-995-9801	E-Mail Address (if available) corcoran.andrea@idenix.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

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## EXCLUSIVITY SUMMARY

NDA # 22-011

SUPPL # n/a

HFD # 530

Trade Name Tyzeka

Generic Name Telbivudine

Applicant Name Idenix Pharmaceuticals

Approval Date, If Known October, 2006

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1

YES

Explain:

!  
!

! NO

! Explain:

Investigation #2

YES

Explain:

!  
!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

---

Name of person completing form: Kenny Shade  
Title: Regulatory Health Project Manager  
Date: 10/3/2006

Name of Office/Division Director signing form: Debra Birnkrant  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Debra Birnkrant  
10/25/2006 11:57:22 AM  
NDA 22-011

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

ANDA/BLA #: 22-011 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 12/30/2005 PDUFA Goal Date: October 30, 2006

HFD 530 Trade and generic names/dosage form: Tyzeka (telbivudine) 600 mg Film coated tablet

Applicant: Idenix Pharmaceuticals Therapeutic Class: Antiviral

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next section.
- No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): None, new NDA

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation.

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. Birth Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 16 Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies (fill in applicable criteria below):

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

NDA 22-011

Page 3

This page was completed by:

*{See appended electronic signature page}*

Kenny Shade

Regulatory Project Manager

cc: NDA 22-011

HFD-960/ Rosemary Addy or Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG  
DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 6-23-2005)

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/s/

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Kenny Shade  
10/25/2006 01:15:35 PM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN  
SERVICES  
FOOD AND DRUG ADMINISTRATIONPRESCRIPTION DRUG USER FEE  
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS IDENIX PHARMACEUTICALS INC Chuck Miller 60 Hampshire St Cambridge MA 02139 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 022-011	
2. TELEPHONE NUMBER 617-995-9853		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:	
3. PRODUCT NAME Telbivudine		6. USER FEE I.D. NUMBER PD3006347	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO			
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448 Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Jack Hall</i>		TITLE VP, REGULATOR AFFAIRS	DATE DEC. 1, 2005
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$767,400.00			
Form FDA 3397 (12/03)			

( BE PRMT CLOSE G ) ( Print Cover sheet )

## Debarment Certification

Idenix Pharmaceuticals, Incorporated hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

David Hall = Date 9 Dec., 2005

David Hallinan, PhD.

Vice President, Regulatory Affairs

Idenix Pharmaceuticals, Inc.



FDA Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia,  
and Rheumatologic Products  
White Oak Bldg #22  
10903 New Hampshire Ave, Silver Spring, MD 20993

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**Response to Consultation Request**

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**Date:** October 2, 2006

**To:** Kenny Shade  
Charlene Brown M.D.,  
Medical Officer  
Division of Antiviral Products

**From:** Keith K. Burkhart, MD  
Medical Officer

**Through:** Keith Hull, MD, PhD  
Team Leader  
DAARP  
Rigoberto Roca, M.D., Deputy Director  
DAARP

Bob Rappaport, M.D., Director  
DAARP

**Subject:** Consult on NDA 22-011  
Tyzeka (telbivudine)

**Date of Consultation:** 9/22/2006

**Date Response Requested  
(Priority):** 10/2/2006

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**The Division of Antiviral Products (DAP) has consulted the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding the association between the synthetic nucleoside analogue telbivudine (LdT) and elevations in creatinine kinase (CK) elevations and symptoms of myopathy. DAP has provided a summary of the their review of the clinical studies involving LdT and lamivudine (LAM) and have asked four questions:**

- 1. Does DAARP agree that there is a likely drug-association between LdT and myopathy?**
- 2. How does DAARP interpret the higher rate of CK elevations among subjects on LdT, the relatively similar rates (between study arms) of muscle-related symptoms among subjects with CK elevations, and the relatively imperfect relationship between CK elevations and myopathy among the subjects who experienced muscle weakness?**
- 3. Does DAARP agree with DAP's proposed language for the Warnings section of the LdT label? If not, please suggest appropriate language.**
- 4. DAP requests any other insights or comments that DAARP may have regarding the adverse event profile of LdT.**

Myopathy is a general term referring to any skeletal muscle disorder with structural changes or functional impairment of the muscle. The most common symptom of patients with myopathy is muscle weakness which can be either intermittent or persistent in nature. Drug-induced injury to muscle is a well-known etiology of myopathy and can be mediated directly by toxic damage to the muscle fibers (e.g., alcohol, cocaine, lovastatin, clofibrate) or by blocking metabolic muscle energy sources and mitochondrial damage. Additionally, certain drugs (e.g., procainamide, phenytoin, and zidovudine) can result in myositis, which is characterized by interstitial or perivascular inflammation. Symptoms from drug-induced myopathies can range from transient mild myalgias to chronic severe weakness. Regardless of the etiology of the myopathy, the laboratory hallmark of muscle damage is elevations in serum CK concentrations. CK elevations may represent early injury that has not progressed to symptomatic disease; however, the converse may also be true, as patients may develop myopathy with little if any CK elevation. While elevations in skeletal muscle-derived CK levels may be physiologic, they are generally thought to be indicative of underlying muscle damage. Clinically, electromyography can be helpful in determining the type of myopathy but muscle biopsy remains the gold standard.

Drug-induced myopathy with the nucleoside analogues was noted when the NRTI zidovudine first came to market. Zidovudine-induced myopathy results from the inhibition of DNA polymerase gamma that ultimately results in mitochondrial DNA depletion. Since LdT experimentally inhibits viral, but not human DNA polymerase, it was thought that LdT would not be associated with myopathy. Further study has shown that many other mechanisms can lead to mitochondrial toxicity including; adversely affecting mitochondrial RNA, nucleotide phosphorylation and the mitochondrial respiratory chain. [Cote HCF. Possible ways nucleoside analogues can affect mitochondrial DNA content and gene expression during HIV therapy. *Antiviral Therapy* 2005;10 (suppl 2):M3-M11].

The data provided by DAVP demonstrate that new-onset CK elevations, Grades 1-4, were higher in LdT-treated patients (72%) compared to LAM-treated patients (42%) during the first year while on active treatment. A total of 9% of LdT treated-patients developed new onset Grade 3 or 4 CK elevations compared to 3% of LAM-treated patients. The Kaplan-Meier plot of time to onset of new-onset Grade 1-4 CK elevations demonstrated that CK levels were similar between the treatment arms until the incidence appeared to gradually increase among LdT-treated patients relative to LAM-treated patients after approximately 100-150 days on study drug. Analysis showed that the higher incidence of CK elevations among LdT-treated patients continued to increase compared to LAM-treated patients, until reaching a plateau at one year of therapy. In cases where LdT was discontinued or treatment interrupted there appeared to be a universally associated fall in the CK values.

As discussed above, nucleoside analogues have been associated with myopathy. Dr. Charlene Brown performed a thorough analysis examining patients with a possible muscle-related AE within +/- 30 days of a Grade 1-4 CK elevation. Results of the analysis are as follows:

- Grade 1-4 CK elevation: LdT (8%) vs. LAM (6%)
- Grade 1-2 CK elevation: LdT (7%) vs. LAM (6%)
- Grade 3-4 CK elevation: LdT (1%) vs. LAM (1%)

These data suggest that despite the higher proportion of LdT-treated patients with CK elevations there does not appear to be a substantial difference in the development of clinical symptoms compared to LAM-treated patients. However, more patients on LdT than LAM discontinued or interrupted study drug due to CK elevations. Most patients who discontinued study drug had developed musculoskeletal related symptoms. We agree with Dr. Brown's conclusions that the higher frequency of study drug discontinuations due to CK elevations for LdT-treated patients may be a consequence of physicians detecting and intervening because of the higher frequency of CK elevations among LdT-treated patients. However, it is interesting to note that a greater portion of LdT-treated patients (0.8%) developed an AE associated with the specific symptom of muscle weakness compared to LAM-treated patients (0.2%). The median time to onset of muscle weakness was 261 days. Although a decrease of CK levels and a clinical improvement in symptoms were generally seen following LdT discontinuation, at least two patients had continued clinical evidence of myopathy one year after discontinuation of the drug.

The mechanism whereby LdT is exerting its effect on muscle is not clearly understood. As mentioned above, it was originally thought because of LdT selectivity that the risk of myopathy should be decreased but clearly the results do not support this theory. The Case Reports which describe biopsy results do not support an inflammatory or autoimmune mechanism for the myopathy. Subject #012-001 had a muscle biopsy that demonstrated myofibrillary degeneration. Subject # 010-023 on biopsy had partial muscle fibrosis, mild muscle atrophy and rhabdomyolysis. Thus it is unlikely that LdT is being mediated via an inflammatory or autoimmune process.

The Case Reports described in the consultation, raise additional questions as well. It is not clear what the best course of action should be when a patient develops symptoms and/or CK

elevations. Subject # 010-023 is a case in point. This patient appears to have been successfully treated, although further follow-up is needed. This subject's CK did return to normal with what might be described as therapy to treat mitochondrial toxicity; ATP and CoA. The literature does contain other reports of the treatment of NRTI-induced mitochondrial toxicity with Coenzyme Q. Likewise case # 132-002 may demonstrate that only temporary interruption of therapy is needed, although additional follow-up is lacking in the report.

**Summary Conclusions to Questions from DAP:**

1. DAARP agrees that there is a strong association between LdT and elevations in CK levels and myopathy.
2. Skeletal muscle-associated CK elevations are suggestive of muscle damage, especially in patients who had previously had normal baseline values. However, CK elevations may represent early injury that has not progressed to symptomatic disease or may not progress to a level where the muscle damage is clinically symptomatic. The converse may also be true, as patients may develop myopathy with little if any CK elevation. Although the data from the sponsor's submission clearly demonstrates that a greater proportion of LdT-treated patients developed CK elevations compared to LAM-treated patients, it is difficult to explain the relatively similar development rate of myopathy symptoms. Although a slightly higher percentage of LdT patients developed symptoms of myopathy it was not to the same degree that they developed elevations in CK levels. It is difficult to explain these results but it may relate to the underlying mechanisms whereby the drugs induce their muscle toxicity. Theoretically, patients with CK elevations may represent an at risk population. These patients may remain susceptible to an oxidant stress or other precipitating factor that when encountered may worsen mitochondrial toxicity and lead to myopathy.
3. In general we agree with your suggested label changes but recommend you remove the term "myositis" from the proposed language for the following reasons. First, myopathy is a very broad term that encompasses the etiologies that may be responsible for the cases of elevated CKs and patients' symptoms. Secondly, the term myositis connotes a specific clinical disorder that requires specific therapy. From our reading of the case reports provided in your review there were no biopsy-confirmed cases of myositis (typically characterized by peri-fascicular or perivascular infiltrates of lymphs and/or neutrophils and/or eosinophils). Additionally, although there were a large proportion of patients presenting with elevated CKs, only a minority of these patients were symptomatic. It may be of use to specifically state in the label the proportion of patients presenting with an elevated CK compared to controls and what proportion of them developed clinical symptoms and how they responded after withdrawal of telbivudine. This will provide a treating physician with more data when deciding whether telbivudine should be stopped in a patient responding to the drug but who has developed elevated CKs with or without symptoms of a myopathy. Finally, consider noting that muscle pain may also include unexplained chest and abdominal pain.

4. We also agree that post-marketing studies should be performed that carefully evaluate outcomes in patients who develop CK elevations and symptoms of myopathy while receiving treatment with LdT. Monitoring for predisposing and precipitating factors should be tracked through the case report forms. Consider defining a cohort of patients who would have EMGs and possibly muscle biopsies performed to help understand the pathophysiology. Consider following all patients for resolution of their myopathy to determine if some patients do suffer irreversible myopathic disease.

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/s/

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Keith K Burkhardt  
11/9/2006 11:48:41 AM  
MEDICAL OFFICER

No changes from last draft review 11/9/06

Keith Hull  
11/9/2006 01:47:59 PM  
MEDICAL OFFICER

Bob Rappaport  
11/9/2006 06:11:52 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

October 27, 2006

NDA 22-011

Idenix Pharmaceuticals Inc.  
Attention: David Hallinan, Ph. D  
Vice President, Regulatory Affairs  
60 Hampshire Street  
Cambridge, MA 02139

Dear Dr. Hallinan:

Please refer to your new drug application (NDA) for Tyzeka (telbivudine) 600 mg tablets approved on October 25, 2006.

As discussed via telephone on October 26, 2006 between David Hallinan and Kenny Shade of this Division, the approval letter issued for NDA 22-011 on October 25, 2006 inadvertently contained language citing 21 CFR 314.550 which is a regulation regarding the submission of promotional materials for products approved under accelerated approval. This NDA was not governed by this regulation and this letter is being sent with the appropriate language that should have been included in your approval letter.

The appropriate language for that section of the approval letter should read:

“In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/the Division of Antiviral Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Kenny Shade, Regulatory Project Manager, at 301-827-2335.

Sincerely,

*{See appended electronic signature page}*

Jeffrey Murray, MD  
Acting Deputy Office Director  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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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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Jeffrey Murray  
10/27/2006 12:37:32 PM

## ACTION PACKAGE CHECKLIST

Application Information		
BLA # n/a NDA # 22-011	BLA STN# n/a NDA Supplement # n/a	If NDA, Efficacy Supplement Type n/a
Proprietary Name: Tyzeka Established Name: telbivudine Dosage Form: 600 mg tablet		Applicant: Idenix Pharmaceuticals
RPM: Kenny Shade		Division: Antiviral Products      Phone # 301-796-0807
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):  n/a  Provide a brief explanation of how this product is different from the listed drug. n/a  <input type="checkbox"/> If no listed drug, check here and explain:  <b>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</b>  <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		October 30, 2006
❖ Action Goal Date (if different)		October 25, 2006
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):      Type 1	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	
BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies	
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Alert



notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	Included
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	n/a
<b>Labeling</b>	
❖ Package Insert	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	Included 10/23/2006
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	n/a
❖ Patient Package Insert	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included 10/4/2006
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	n/a
❖ Medication Guide	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	n/a
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	Included 10/18/2006

❖ Labeling reviews and minutes of any labeling meetings ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> DMETS <input checked="" type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> Other reviews DSI consult and Division of Anesthesia, Analgnesia, & Rheumatology consult <input type="checkbox"/> Memos of Mtgs
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<b>Administrative Documents</b>	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	Included
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If AP: OC clearance for approval</li> </ul>	N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	Included in approval letter.
<ul style="list-style-type: none"> <li>• Incoming submission documenting commitment</li> </ul>	October 23.,2006
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	September 25, 2006
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg      April 5, 2005
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg      June 17, 2002
<ul style="list-style-type: none"> <li>• Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	November 13, 2002
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date of Meeting</li> </ul>	n/a
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available</li> </ul>	n/a
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	n/a
<b>CMC/Product Quality Information</b>	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	Included
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <li>• <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• <input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• <input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	

❖ NDAs: Microbiology reviews (sterility & apyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not a parenteral product
Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: March 17, 2006 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review <i>(indicate date(s))</i></li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) <i>(indicate date completed, must be within 60 days prior to AP)</i></li> </ul>	n/a <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

**Nonclinical Information**

❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Included
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None      CAC
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc      Included
❖ ECAC/CAC report/memo of meeting	Included
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested

**Clinical Information**

❖ Clinical review(s) <i>(indicate date for each review)</i>	Included
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed
❖ Safety Update review(s) <i>(indicate location/date if incorporated into another review)</i>	
❖ Risk Management Plan review(s) (including those by OSE) <i>(indicate location/date if incorporated into another review)</i>	
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i>	<input type="checkbox"/> None requested
• Clinical Studies	Included
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None      Included
❖ Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None      Included

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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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Kenny Shade  
10/25/2006 01:10:21 PM

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-011

Supplement # N/A

Efficacy Supplement Type SE- N/A

Trade Name: Tyzeka™

Established Name: Telbivudine

Strengths: 600 mg tablet

Applicant: Idenix Pharmaceuticals

Agent for Applicant: David Hallinan

Date of Application: December 30, 2005

Date of Receipt: December 30, 2005

Date clock started after UN:

Date of Filing Meeting: February 21, 2006

Filing Date: February 28, 2006

Action Goal Date (optional):

User Fee Goal Date: October 30, 2006

Indication(s) requested: Treatment of chronic hepatitis B in patients with evidence of viral replication

Type of Original NDA: (b)(1)  (b)(2)   
OR

Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR  NDA is a (b)(2) application

Therapeutic Classification: S

P

Resubmission after withdrawal?

Resubmission after refuse to file?

Chemical Classification: (1,2,3 etc.) 1

Other (orphan, OTC, etc.) n/a

Form 3397 (User Fee Cover Sheet) submitted:

YES  NO

User Fee Status:

Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format? All

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO
- Is it an electronic CTD (eCTD)? N/A  YES  NO   
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES, \_\_\_\_\_ Years NO   
**NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.**
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
**NOTE:** Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y  NO
- PDUFA and Action Goal dates correct in COMIS? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. [Requested document room to change name from Sebivo to Tyzeka]
- List referenced IND numbers: 60,459
- End-of-Phase 2 Meeting(s)? Date(s) June 17, 2002 NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) April 5, 2005 NO   
If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic "Content of Labeling" submitted? YES  NO   
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES  NO
- Risk Management Plan consulted to ODS/IO? N/A  YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES  NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
- Has DOTCDP been notified of the OTC switch application? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: February 21, 2006

**BACKGROUND:**

(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

**ATTENDEES:**

**ASSIGNED REVIEWERS (including those not present at filing meeting) :**

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Charlene Brown, M.D.
Secondary Medical:	
Statistical:	Fraser Smith, Ph.D.
Pharmacology:	Ita Yuen, Ph.D.
Statistical Pharmacology:	
Chemistry:	Ko-Yu Lo, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Jenny H. Zheng, Ph.D.
Microbiology, sterility:	Sung Rhee, Ph.D.
Microbiology, clinical (for antimicrobial products only):	
DSI:	Antiono El Hague
Regulatory Project Management:	Kenny Shade, J.D., B.S.N.
Other Consults:	DMETS/DSI/Division of Anesthesia, Analgesia & Rheumatology Products.

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

• Clinical site inspection needed? YES X NO

• Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

• Biopharm. inspection needed? YES  NO

PHARMACOLOGY

N/A

FILE

REFUSE TO FILE

- GLP inspection needed?

YES

NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection?
- Microbiology

YES

NO

YES

NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3.  Convey document filing issues/no filing issues to applicant by Day 74.

Kenny Shade, J.D., B.S.N.  
Regulatory Project Manager, HFD-530

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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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Kenny Shade  
10/25/2006 02:22:17 PM  
CSO

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** October 4, 2006

**TO:** Debra Birnkrant, M.D., Director  
Division of Antiviral Products

**VIA:** Kenny Shade, J.D., B.S.N., Regulatory Health Project Manager,  
Division of Antiviral Products

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support

**THROUGH:** Toni Piazza-Hepp, Pharm.D., Deputy Director  
Division of Surveillance, Research, and Communication Support

**SUBJECT:** DSRCs Review of Patient Labeling for Tyzeka (telbivudine)  
Tablets, NDA 22-011

The sponsor submitted a draft Patient Package Insert (PPI) for review for Tyzeka (telbivudine) Tablets, NDA 22-011, October 3, 2006, (original NDA was submitted December 30, 2005).

We have reviewed the draft PPI and find it acceptable. It is consistent with the Prescriber Information (PI), is in a Medication Guide question and answer type format (not required for, but recommended for all patient information), and is written at an appropriate reading level for patient materials (Flesch-Kincaid Reading level is 7.8 and the Flesch Reading Ease is 60.6%).

Please call us if you have any questions.

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/s/

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Jeanine Best  
10/4/2006 01:18:23 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
10/6/2006 11:27:37 AM  
DRUG SAFETY OFFICE REVIEWER

## REQUEST FOR CONSULTATION

TO (Office/Division): Division of Surveillance, Research, and Communications

FROM (Name, Office/Division, and Phone Number of Requestor): Kenny Shade/Division of Antiviral Products/301-796-0807

DATE  
October 3, 2006

IND NO.

NDA NO.  
22-011

TYPE OF DOCUMENT  
Patient Package Insert

DATE OF DOCUMENT  
October 3, 2006

NAME OF DRUG  
Tyzeka

PRIORITY CONSIDERATION  
High

CLASSIFICATION OF DRUG  
Antiviral

DESIRED COMPLETION DATE  
October 11, 2006

NAME OF FIRM: Idenix Pharmaceuticals Inc. [Sponsor contact: David Hallinan 617-995-9907]

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review enclosed Patient Package Insert.

SIGNATURE OF REQUESTOR  
Kenny Shade

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Kenny Shade  
10/3/2006 10:27:57 AM

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**CLINICAL INSPECTION SUMMARY**

**DATE:** September 15, 2006

**TO:** Kenny Shade, Regulatory Project Manager  
Charlene Brown, M. D., Medical Officer  
Division of Antiviral Drug Products, HFD-530

**THROUGH:** Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

**FROM:** Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22-011

**APPLICANT:** Idenix

**DRUG:** Telbivudine

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of Compensated Chronic Hepatitis B.

**CONSULTATION REQUEST DATE:** March 10, 2006

**DIVISION ACTION GOAL DATE:** October 16, 2006

**PDUFA DATE:** October 30, 2006

**I. BACKGROUND:**

The review division requested inspection of protocol NV-02B-007: A Randomized, Double Blind trial of LdT (Telbivudine) versus Lamivudine in Adults with Compensated Chronic Hepatitis B. The sponsor submitted results of this protocol in support of NDA 22-011. This study was a phase III, randomized, double blind, multicenter international clinical trial designed to compare the efficacy and safety of LdT (600 mg/day) vs. Lamivudine (100 mg/day). The primary efficacy endpoint was histologic improvement at 52 weeks defined as >2 point decrease in Knodell necroinflammatory score with no worsening in fibrosis. Secondary endpoints include improvement in Ishak fibrosis score, change in HBV DNA by bDNA assay and by PCR assay, normalization of ALT, and loss of HbeAg.

The following four foreign sites were selected for data audit in support of this application:

Site# 008 (Yun-Fan Liaw, M.D.- Taiwan, Republic of China)

Site# 50 (Sawat Thongsawat, M.D.-Chaing Mai, Thailand)

Site# 041 (William Seivert, M.D.- Clayton , Australia)

Site# 057 (Edward Gane, M.D.- Auckland, New Zealand)

The inspections targeted four clinical investigators who enrolled a relatively large number of subjects.

## II. RESULTS (by protocol/site):

Name of CI and site #, if known	Country	Protocol	Insp. Date	EIR Received Date	Final Classification
Yun-Fan Liaw, M.D.	Taiwan	NV-02B-007	6/19/06	8/23/06	NAI
Sawat Thongsawat, M.D.	Thailand	NV-02B-007	6/26/06	8/23/06	NAI
William Seivert, M.D.	Australia	NV-02B-007	7/3/06	8/23/06	NAI
Edward Gane, M.D.	New Zealand	NV-02B-007	7/10/06	8/23/06	VAI

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

### Protocol NV-02B-007

#### 1. Yun-Fan Liaw, M.D.

At this site a total of 93 subjects were screened, 35 subjects were reported as screen failures and 62 subjects were enrolled in protocol NV-02B-007. Nine subjects were reported as discontinued due to consent withdrawal (044, 079), lost to follow-up (061), transfer to another site (050), elevated HBV-DNA levels (022, 029, 036) and elevated ALT levels (002, 036).

Informed consent for all subjects was verified and no regulatory violations found. The medical records were reviewed in depth and compared source data, case report forms to data listings for primary efficacy endpoint and adverse events for 20 subjects in study protocol NV-02B-007. The adverse events experienced by study subjects during the study were accurately reported in the case report forms and to the IRB in a timely manner.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Satawat Thongsawat, M.D.

At this site a total of 80 subjects were screened; 29 subjects were reported as screen failures; four subjects withdrew consent, and 51 subjects were randomized in protocol NV-02B-007. Informed consent for all subjects was verified and no regulatory violations found. The medical records were reviewed in depth and compared source data, case report forms to data listings for primary efficacy endpoint and adverse events for 20 randomized subject files enrolled in protocol NV-02B-007. The adverse events experienced by study subjects during the study were accurately reported in the case report forms and to the IRB in a timely manner.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

3. William Sievert, M.D.

At this site a total of 31 subjects were screened, 9 subjects were reported as screen failures, two subjects were discontinued early to raise a family, one subject transferred, and 22 subjects were enrolled in protocol NV-02B-007. Informed consent for all subjects was verified and no regulatory violations found. The medical records were reviewed in depth and compared source data, case report forms to data listings for primary efficacy endpoint and adverse events for 22 subjects in study protocol NV-02B-007. The adverse events experienced by study subjects during the study were accurately reported in the case report forms and to the IRB in a timely manner.

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

4. Edward Gane, M.D.

At this site a total of 132 subjects were screened, 67 subjects were reported as screen failures, 13 subjects were discontinued for disease conditions, 11 subjects for adverse events, 3 subjects were transferred to other sites, and 62 subjects were enrolled in protocol NV-02B-007. Informed consent for all subjects was verified and no regulatory violations found. The medical records were reviewed in depth and compared source data, case report forms to data listings for primary efficacy endpoint and adverse events for 22 subjects in study protocol NV-02B-007. The adverse events experienced by study subjects during the study were accurately reported in the case report forms and to the IRB in a timely manner (except for three subjects: subjects 008, 045 and 0101 experienced an elevated liver function tests during the study and these events were not reported to the sponsor as adverse events).

The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that impact the results. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

## OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Liaw, Thongsawart, Sievert and Gane did not identify any significant observations that would compromise the integrity of the data. As noted above, observations found in Dr. Gane's report regarding the non-reporting of adverse events (flare) for three subjects will be included in the letter to the clinical investigator under failure to adhere to the protocol. Overall, the data appear acceptable in support of the pending application.

Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations

## CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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/s/

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Antoine El-Hage  
9/22/2006 08:38:40 AM  
PHARMACOLOGIST

Constance Lewin  
9/25/2006 01:21:14 PM  
MEDICAL OFFICER



Edward J. Gane, M.D.  
Hepatitis Research Clinic Gastroenterology  
Bldg 15, Middlemore Hospital  
Private Bag 93311, Otahuhu  
Auckland, New Zealand

Dear Dr. Gane:

Between July 10 and 12, 2006, Ms. Barbara J. Breithaupt, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol NV-02B-007 entitled: "A Randomized, Double Blind Trial of LdT (Telbivudine) versus Lamivudine in Adults with Compensated Chronic Hepatitis B") of the investigational drug Telbivudine, performed for Idenix Pharmaceuticals, Inc..

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

We understand that you conducted the study under a U.S. Investigational New Drug Application (IND) and thus, is subject to the U.S. Code of Federal Regulations (CFR). Therefore, we are providing comments so that you will be aware of FDA's requirements for clinical trials conducted under a U.S. IND.

We provide these comments based on our review of the establishment inspection report, and the documents submitted with that report. The provisions of the U.S. Code of Federal Regulations (CFR) that were violated for the study conducted under an IND are provided below for future reference. We wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

The protocol specified that all adverse events regardless of relationship to study drug, are to be reported to the sponsor on the adverse events section of the case report form. Our investigation found that, in at least three subjects, the adverse events were not reported to the sponsor:

Subject# 008 had an ALT liver enzyme value of 118 IU/L at baseline. This liver function test increased to 341 IU/L at week 40. The increase in liver enzyme was not reported in the adverse event section of the case report form.

Subject# 045 had an ALT liver enzyme value of 54 IU/L at baseline. This liver function test increased to 311 IU/L at week 40. The increase in liver function test was not reported in the adverse event section of the case report form.

Subject# 101 had an ALT liver enzyme value of 110 IU/L at baseline. This liver function test increased to 605 IU/L at week 68. The increase in liver function was not reported in the adverse event section of the case report form.

Please make the appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Breithaupt during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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/s/

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Constance Lewin  
9/25/2006 01:27:30 PM

**REQUEST FOR CONSULTATION**

TO (Office/Division): Division of Anesthesia, Analgesia, & Rheumatology Products

FROM (Name, Office/Division, and Phone Number of Requestor): Kenny Shade, Division of Antiviral Products/301-796-0807

DATE  
September 22, 2006

IND NO.

NDA NO.  
22-011

TYPE OF DOCUMENT  
Attachment with background

DATE OF DOCUMENT

NAME OF DRUG  
Tyzeka (telbivudine)

PRIORITY CONSIDERATION  
High

CLASSIFICATION OF DRUG  
Antiviral

DESIRED COMPLETION DATE  
October 2, 2006

NAME OF FIRM: Idenix Pharmaceuticals/ Contact: David Hallinan, PhD, 617-995-9907

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

**II. BIOMETRICS**

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

**III. BIOPHARMACEUTICS**

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

**IV. DRUG SAFETY**

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Thank you for your willingness to help us interpret this relatively rare finding of myopathy among subjects on telbivudine (NDA 22-011). Attached is a document that attempts to provide limited background and summarize relevant issues. We apologize for the very short time-frame associated with this consult request, but given that we have commenced labeling negotiations and our upcoming PDUFA date is October 30th, would appreciate your comments as soon as possible (preferably by COB on October 2nd).

- Do you agree that there is a likely drug-association between telbivudine (LdT) and myopathy?
  - How do you interpret the higher rate of CK elevations among subjects on LdT, the relatively similar rates (between the study arms) of muscle-related symptoms among subjects with CK elevations, and the relatively imperfect relationship between CK elevations and myopathy among the subjects who experienced muscle weakness (see section: Drug-Associated Myopathy: Muscle Weakness in attached document)?
  - Do you agree with our proposed language(at the end of the attached document) for the warnings section of the Telbivudine label? If not, please suggest appropriate language.
  - We welcome any other insights or comments that you may have regarding this adverse event profile.
- Again, thank you for your attention and I am available for informal clarifications or discussions related to this consult. We look forward to your inputs.

SIGNATURE OF REQUESTOR Kenny Shade	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

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Kenny Shade  
9/22/2006 12:54:39 PM



Yun-Fan Liaw, M.D.  
Liver Research Unit  
Chang Gung Memorial Hospital  
5, Fu-Shing Street, Kweishan  
Taoyuan, 333 Taiwan  
Republic of China

Dear Dr. Liaw:

Between June 19 and 22, 2006, Ms. Barbara J. Breithaupt, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol NV-02B-007 entitled: "A Randomized, Double Blind Trial of LdT (Telbivudine) versus Lamivudine in Adults with Compensated Chronic Hepatitis B") of the investigational drug Telbivudine, performed for Idenix Pharmaceuticals, Inc..

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Breithaupt during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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/s/

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Constance Lewin  
9/15/2006 12:27:45 PM



William Sievert, M.D.  
Department of Medicine  
Monash Medical Center  
246 Clayton Road  
Clayton, Victoria 3168  
Australia

Dear Dr. Sievert:

Between July 3 and 5, 2006, Ms. Barbara J. Breithaupt, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol NV-02B-007 entitled: "A Randomized, Double Blind Trial of LdT (Telbivudine) versus Lamivudine in Adults with Compensated Chronic Hepatitis B") of the investigational drug Telbivudine, performed for Idenix Pharmaceuticals, Inc..

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Breithaupt during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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/s/

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Constance Lewin  
9/15/2006 12:14:06 PM



Satawat Thongsawat, M.D.  
Chiang Mai University Hospital, Sri-Pat Bldg.  
Department of Medicine, Gastroenterology  
Chiang Mai, 50200  
Thailand

Dear Dr. Thongsawat:

Between June 26 and 29, 2006, Ms. Barbara J. Breithaupt, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol NV-02B-007 entitled: "A Randomized, Double Blind Trial of LdT (Telbivudine) versus Lamivudine in Adults with Compensated Chronic Hepatitis B") of the investigational drug Telbivudine, performed for Idenix Pharmaceuticals, Inc..

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Breithaupt during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I, HFD-46  
Division of Scientific Investigations  
Office of Compliance  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

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/s/

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Constance Lewin  
9/15/2006 12:20:51 PM



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011  
**Drug:** Tyzeka™ (telbivudine)  
**Date:** September 15, 2006  
**To:** David Hallinan, Ph.D.  
**Sponsor:** Idenix Pharmaceuticals, Inc.  
**From:** Kenny Shade, JD, BSN  
**Through:** Jenny H. Zheng, PhD  
**Concur:** Russell Fleischer, PA-C, MPH  
Kellie Reynolds, PharmD  
**Subject:** Clinical Pharmacology Comments

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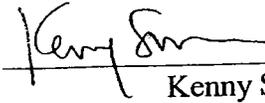
The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for Tyzeka™ submitted December 30, 2005.

**Clinical Pharmacology Comments**

1. Please provide extended long-term stability data that cover the period from sample collection to the end of sample analysis. We found that in some studies (e.g., telbivudine plasma samples for Studies NV-02B-012 and NV-02B-013, and telbivudine urine samples for Study NV-02B-006), the period with stability data provided is shorter than the sample storage period.
2. Please provide stability data for peginterferon alfa-2a for Study NV-02B-012.
3. Please explain why the PK exposures after 600 mg once daily dose for 7 days are much lower in the QT study (NV-02B-024) as compared to other studies.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

September 14, 2006



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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
9/15/2006 07:28:08 AM  
CSO

Russell Fleischer  
9/15/2006 08:14:41 AM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration  
Division of Antiviral Products  
Office of Antimicrobial Products  
Silver Spring, MD 20903

**Date:** September 11, 2006  
**IND:** 22-011  
**Drug:** Telbivudine (LdT)  
**To:** David Hallinan, PhD  
**Sponsor:** Idenix Pharmaceuticals  
**From:** Kenny Shade, JD, BSN  
**Through:** Charlene Brown, MD  
**Concurrence:** Russell Fleischer, PA-C, MPH  
**Subject:** Clinical Comments

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The following comments are being conveyed to you on behalf of the review team. Please refer to your NDA 22-011 submitted on December 30, 2005.

Clinical Comments

1. In Please clarify how you obtained the values in Table 14.1.3.3 for the Safety Evaluable Population (All Visits) from the NV-02B-007 Study Report. I have reviewed the electronic listings datasets (DISC, STUDYSUM, AE) but I cannot seem to obtain the same results.

Thank you and we look forward to your reply by COB on Tuesday, September 12, 2006 and cc Charlene Brown at Charlene.Brown@fda.hhs.gov

We are providing this above information via telephone facsimile for your convenience.

**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
9/11/2006 09:51:44 AM  
CSO

Russell Fleischer  
9/11/2006 10:46:35 AM  
MEDICAL OFFICER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011  
**Drug:** SEBIVO™ (telbivudine)  
**Date:** August 28, 2006  
**To:** David Hallinan, Ph.D.  
**Sponsor:** Idenix Pharmaceuticals, Inc.  
**From:** Kenny Shade, JD, BSN  
**Through:** Charlene Brown, M.D., Clinical Reviewer  
**Concur:** Katherine Laessig, MD, Clinical Team Leader  
**Subject:** Name Review Comments

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The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for Sebivo™ submitted December 30, 2005.

**Trade Name Review Comments**

Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the proprietary name Sebivo. In reviewing the proprietary names, the primary concerns related to look-alike and /or sound-alike confusion with Sustiva. DMETS has no objections to the use of the proprietary name, Tyzeka.

Sustiva was identified as having orthographic similarity with Sebivo. Additionally, one respondent in the inpatient prescription study misinterpreted the name Sebivo as Sustiva. Sustiva is an antiretroviral agent indicated for the treatment of HIV infection. The recommended adult dose is 600 mg once daily in combination with other antiretroviral agents.

Both names begin with the letter "S". Additionally, Sustiva contains the upstroke letter "t" which can look like the upstroke letter "b" in Sebivo when the letter "t" is not crossed. The last three letters of both names may also look similar ("ivo" vs "iva"). Furthermore, the letter "o" may look like the letter "a" if a loop is made on the last stroke. Conversely, the letter "e" in Sebivo does not look like the letters "us" in Sustiva which may help to differentiate the names. However, there are several product characteristics which may increase the potential for confusion between the two names. Both Sustiva and Sebivo have

overlapping characteristics such as dosage form (tablet), route of administration (oral), dose (600 mg), strength (600 mg), and frequency of administration (once daily). Thus, both products can be ordered as: 600 mg, 1 daily, #30. These shared product characteristics in conjunction with look-alike properties of the names may increase the potential for confusion. Additionally, the patient population and prescriber population may overlap since those infected with the HIV-1 virus may also be infected with the Hepatitis B virus. Orthographic similarities between the names coupled with overlapping product characteristics may increase the potential for confusion between the name pair.

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified several areas of possible improvement, which might minimize potential user errors.

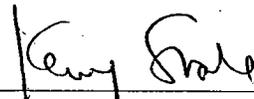
1. CONTAINER LABEL

Increase the prominence of the established name.

2. INSERT LABELING

- a. The abbreviations “ $\mu$ M” and “ $\mu$ g” are used in the insert labeling. The abbreviation “ $\mu$ ” may be mistaken for the letter “m” and be misinterpreted as meaning “milli”, thus leading to misinterpretations of the information presented. This abbreviation appears on the Institute for Safe Medication Practices (ISMP) list of dangerous abbreviations. In June 2006, the FDA and the ISMP launched a nationwide health professional education campaign aimed at reducing the number of common but preventable sources of medication mix-ups and mistakes caused by the use of unclear medical abbreviations. Thus we request that OND and pharmaceutical companies not approve or use abbreviations in the labels and labeling as they can be misinterpreted and contribute to errors. DMETS recommends writing out the abbreviations or revise to read “mcg” rather than “ $\mu$ g”.
- b. In the PRECAUTIONS section under Information for Patients, it states that a patient package insert (PPI) is available. This was not submitted for review and comment. DMETS recommends that DMETS and the Division of Surveillance, Research, and Communication Support (DSRCS) be contacted for a separate review of the PPI when it becomes available.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.



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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
8/31/2006 12:35:54 PM  
CSO

Kathrine Laessig  
9/5/2006 03:06:48 PM  
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: August 21, 2006

TO: Debra B. Birnkrant, M.D.  
Director  
Division of Anti-Viral Products, DAVP

FROM: Michael F. Skelly, Ph.D.  
Pharmacologist  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-011 (Telbivudine  
Tablets), Sponsored by Idenix Pharmaceuticals

At the request of DAVP, the Division of Scientific Investigations audited the clinical and analytical portions of the following bioequivalence study, performed at \_\_\_\_\_

Protocol NV-02B-025

Study# AA26300-01: "A Phase I, Open-Label, Randomized, Three-Way Crossover Study to Evaluate the Bioequivalence among Three Oral Formulations of Telbivudine in Healthy Volunteers"

Following the inspection at \_\_\_\_\_ (7/31 - 8/4/2006), no Form FDA 483 observations concerned this study.

Conclusions:

DSI recommends that the clinical and analytical data from study NV-02B-025/AA26300-01 are acceptable for review.

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/s/

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Amalia Himaya

8/22/2006 02:50:53 PM

CSO

Paper copy signed by Dr. Viswanathan on 8/22/06 and  
available upon request.



Food and Drug Administration  
Division of Antiviral Products  
Office of Antimicrobial Products  
Silver Spring, MD 20903

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011

**Drug:** SEBIVO™ (telbivudine)

**Date:** August 15, 2006

**To:** David Hallinan, Ph.D.

**Sponsor:** Idenix Pharmaceuticals, Inc.

**From:** Kenny Shade, JD, BSN

**Through:** Charlene Brown, M.D., Clinical Reviewer

**Concur:** Katherine Laessig, MD, Clinical Team Leader

**Subject:** Clinical Comments

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The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for Sebivo™ submitted December 30, 2005.

**Clinical Comments**

1. Upon analyzing the data submitted, we found slight differences between the results of our analyses and the demographic and other information described for the HBeAg positive and HBeAg negative subjects in the section of the label described under *Clinical Experience in Patients with Compensated Liver Disease*. We divided subjects for analysis into either HBeAg positive or HBeAg negative based on their assignment in variable STRATE, the lab-based stratum. It is our understanding that, although there were some IVRS errors, these errors did not apply to the assignments made under variable STRATE.

For your reference, the areas of slight discrepancy are as follows:

HBeAg-positive Patients: We found 10% were Caucasian, not 12%  
And we found that the mean serum ALT was 152 IU/L, instead of 146

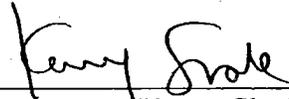
HBeAg-negative Patients:

We found that the 79% of subjects were male, 64% were Asian and 25% were Caucasian, instead of the 77% male, 65% Asian and 23% Caucasian that you describe in the label. We also found the mean serum ALT to be 141 IU/L, not 137 IU/L.

March 14, 2006

These differences are relatively minor, but may point to a misunderstanding of the accuracy of the STRATE variable and we look forward to your clarification. Please clarify by August 23, 2006.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.



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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
8/15/2006 10:06:32 AM  
CSO

Kathrine Laessig  
8/15/2006 10:43:33 AM  
MEDICAL OFFICER

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY  
(DMETS; WO22, Mailstop 4447)**

<b>DATE RECEIVED:</b> August 23, 2005 March 23, 2006	<b>DESIRED COMPLETION DATE:</b> September 9, 2005 July 2006	<b>OSE CONSULT #:</b> 05-0031-1 and 05-0031-2
<b>DATE OF DOCUMENT:</b> August 12, 2005 March 23, 2006	<b>PDUFA DATE:</b> October 30, 2006	

**TO:** Debra B. Birnkrant, MD  
Director, Division of Anti-Viral Drug Products  
HFD-530

**THROUGH:** Linda Y. Kim-Jung, PharmD, Team Leader  
Denise P. Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support

**FROM:** Loretta Holmes, PharmD, Safety Evaluator  
Division of Medication Errors and Technical Support

**PRODUCT NAME:** Sebivo™ (Primary Name)  
Tyzeka™ (Secondary Name)  
(Telbivudine Tablet) 600 mg

**NDA #:** 22-011 (IND# 60,459)

**NDA SPONSOR:** Idenix Pharmaceuticals

**RECOMMENDATIONS:**

1. DMETS does not recommend the use of the proprietary name, Sebivo. However, DMETS has no objections to the use of the proprietary name, Tyzeka. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary names, Sebivo and Tyzeka, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0528.

Division of Medication Errors and Technical Support (DMETS)  
Office of Surveillance and Epidemiology  
HFD-420; White Oak Bldg #22, Mailstop 4447  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** September 12, 2005

**NDA #:** 22-011 (IND# 60,459)

**NAME OF DRUG:** Sebivo™ (Primary Name)  
Tyzeka™ (Secondary Name)  
(Telbivudine Tablet) 600 mg

**IND HOLDER:** Idenix Pharmaceuticals

**\*\*\*NOTE:** This review contains proprietary and confidential information that should not be released to the public.\*\*\*

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530), for assessment of the proprietary names, Sebivo and Tyzeka, regarding potential name confusion with other proprietary or established drug names. This is the second proprietary name submission by the sponsor for this product. The Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the previous name, [REDACTED] because the name was considered misleading and overstated the efficacy of the drug. The Division concurred, therefore, DMETS did not conduct a safety review of [REDACTED]. The sponsor also submitted an independent name analysis conducted by Medical Error Recognition and Revision Strategies, Inc. (Med-E.R.R.S.), a subsidiary of the Institute for Safe Medication Practices, for the proposed tradenames, Sebivo and Tyzeka. The container label and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Sebivo/Tyzeka is the proposed name for telbivudine, a synthetic thymidine nucleoside analogue with specific and selective activity against hepatitis B virus. It is indicated for the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation. The recommended dose is 600 mg once daily, taken orally, with or without food. Dose adjustment is recommended for patients with a creatinine clearance of <50 mL/min. The optimal treatment duration has not been established. Sebivo/Tyzeka will be supplied in bottles of 30 tablets with child-resistant closures.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup>, as well as several FDA databases<sup>3,4</sup> for existing drug names which sound-alike or look-alike to Sebivo and Tyzeka to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. The Saegis<sup>6</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, Sebivo and Tyzeka. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names, Sebivo and Tyzeka, acceptable from a promotional perspective.
2. The Expert Panel identified three proprietary names, two foreign drug names, and one medical term which were thought to have the potential for confusion with Sebivo. The Expert Panel identified four proprietary names which were thought to have the potential for confusion with Tyzeka. These products are listed in Table 1 and Table 2 (pages 4 and 5), along with the dosage forms available and usual dosage.

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<sup>1</sup> MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

<sup>4</sup> Phonetic and Orthographic computer Analysis (POCA)

<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>6</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel (Sebivo)

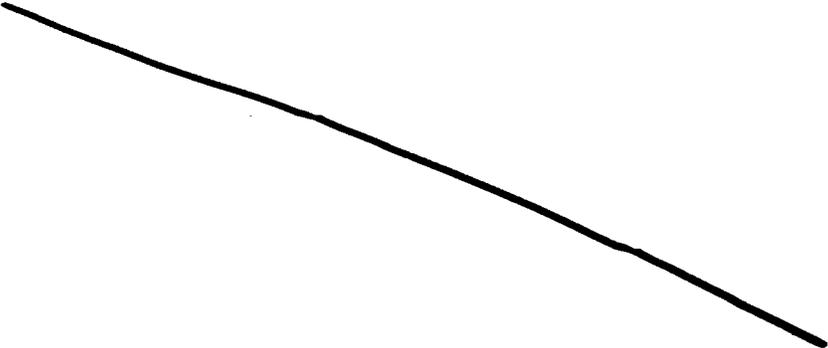
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Sebivo	Tablet Telbivudine 600 mg	<u>Chronic hepatitis B</u> : 600 mg once daily (Dose adjustment is recommended in patients with a creatinine clearance of <50 mL/min.)	N/A
Sustiva	Tablet, capsule Efavirenz Capsule: 50 mg, 100 mg, 200 mg Tablet: 600 mg	<u>HIV-1 infection</u> : 600 mg once daily.	LA
Stalevo 50 Stalevo 100 Stalevo 150	Tablet Carbidopa/Levodopa/Entacapone 12.5/50/200 25/100/200 37.5/150/200	<u>Idiopathic Parkinson's disease</u> : Dose is individualized. Maximum recommended dose is 8 tablets per day with no more than 1 tablet taken at each dosing interval.	SA
			
<p>* Frequently used, not all-inclusive.  ** L/A (look-alike), S/A (sound-alike)  ***Name pending approval. Not FOI releasable.</p>			

Table 2. Potential Sound-alike/Look-Alike Names Identified by EPD (Tyzeka)

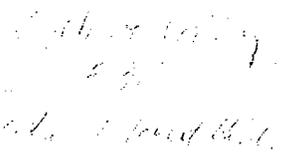
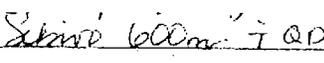
Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Tyzeka	Tablet Telbivudine 600 mg	<u>Chronic hepatitis B</u> : 600 mg once daily (Dose adjustment is recommended in patients with a creatinine clearance of <50 mL/min.)	N/A
Tiazac	Extended-release capsule Diltiazem Hydrochloride 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, and 420 mg	<u>Hypertension</u> : Initially, 120 mg to 240 mg daily, may titrate to a maximum dose of 540 mg once daily <u>Chronic stable angina</u> : Initially, 120 mg to 180 mg once daily, may titrate to a maximum dose of 540 mg once daily	SA
Tyzine Nasal Drops and Nasal Spray	0.1% solution Tetrahydrolazine Hydrochloride 15 mL and 30 mL bottle	<u>Nasal Congestion</u> : Adults: 2-4 drops or 3-4 sprays in each nostril as needed—not more than every 3 hours	LA
Tyzine Pediatric Nasal Drops	0.05% solution Tetrahydrolazine Hydrochloride 15 mL bottle	Children (6 & older): 2-4 drops in each nostril as needed—not more than every 3 hours	
Lyrica	Capsule Pregabalin 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg	<u>Neuropathic pain</u> : 300 mg to 600 mg/day in three divided doses <u>Post-herpetic neuralgia</u> : 150 mg or 300 mg per day in three divided doses <u>Epilepsy</u> : 150 mg to 600 mg per day in 2 or 3 divided doses  (Dose should be adjusted in patients with reduced renal function)	SA
Zyprexa	Tablet Olanzapine 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg	<u>Schizophrenia</u> : Initially, 5 mg to 10 mg once daily. Titrate up to a maximum of 20 mg once daily, if necessary. <u>Bipolar disorder</u> : Initially, 10 mg or 15 mg once daily. Titrate up to a maximum of 20 mg once daily, if necessary.	LA/SA
* Frequently used, not all-inclusive. ** L/A (look-alike), S/A (sound-alike)			

## B. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology for Sebivo and Tyzeka:

Separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Sebivo and Tyzeka with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each study employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription

ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Sebivo and Tyzeka (see below and page 7). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p data-bbox="277 569 446 598"><u>Outpatient RX:</u></p> 	<p data-bbox="852 630 1047 661">"Sebivo 600 mg</p> <p data-bbox="852 703 982 735">Number 30</p> <p data-bbox="852 766 1088 798">Take 1 tablet daily"</p>
<p data-bbox="277 831 430 861"><u>Inpatient RX:</u></p> 	

2. Results for Sebivo:

One respondent in the Sebivo inpatient prescription study misinterpreted the proposed name as Sustiva, a currently marketed product in the United States. One respondent in the outpatient voice study misinterpreted the proposed name as "livido" which sounds similar to the medical term "libido". See Appendix A (page 19) for the complete listing of interpretations from the Sebivo verbal and written studies.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p>Tyzeka 600mg #30 1 daily</p>	<p>“Tyzeka 600 mg Number 30 Take one daily”</p>
<p><u>Inpatient RX:</u></p> <p><del>Tyzeka 600mg 1 daily</del></p>	

3. Results for Tyzeka:

None of the interpretations in the Tyzeka prescription study overlap, sounds similar, or looks similar to any currently marketed U.S. product. See Appendix A (page 20) for the complete listing of interpretations from the Tyzeka verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike/Sound-alike Confusion with Sebivo

In reviewing the proprietary name Sebivo, the primary concerns relating to look-alike and/or sound-alike confusion with Sebivo are: Sustiva, Stalevo, \_\_\_\_\_, \_\_\_\_\_, and the medical terms “cerebral” and “libido”.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Sebivo could be confused with Sustiva as one participant in the written inpatient prescription study misinterpreted the written prescription as Sustiva. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product.

Additionally, one participant in the outpatient verbal study misinterpreted the name as “livido” which sounds similar to the medical term “libido”. The word “libido” is a noun that is defined as “sex drive”. Given the context in which this term would be used, it is unlikely that Sebivo would be confused with “libido”. Therefore, DMETS has no safety concerns with the misinterpretation of the proposed name as “livido” in the verbal prescription study. The medical term “cerebral” was identified by the EPD Panel as having phonetic similarity to Sebivo. “Cerebral” is a medical term meaning “of or relating to the brain or the intellect” and “of, relating to, or being the cerebrum”. Cerebral may sound like Sebivo when spoken. However, because of the context in which the word “cerebral” is likely to be used, it is unlikely that it would be confused with Sebivo.

\*\*\*NOTE: This review contains proprietary and confidential information that should not be released to the public.\*\*\*

The word “cerebral” is an adjective that would likely be used in a sentence or phrase to modify another word. It is unlikely that the word Sebivo would be mistaken for the word “cerebral” if a verbal prescription was given for Sebivo.

- a. Sustiva was identified as having orthographic similarity with Sebivo. Additionally, one respondent in the inpatient prescription study misinterpreted the name Sebivo as Sustiva. Sustiva is an antiretroviral agent indicated for the treatment of HIV infection. The recommended adult dose is 600 mg once daily in combination with other antiretroviral agents.

Both names begin with the letter “S”. Additionally, Sustiva contains the upstroke letter “t” which can look like the upstroke letter “b” in Sebivo when the letter “t” is not crossed. The last three letters of both names may also look similar (“ivo” vs. “iva”). Furthermore, the letter “o” may look like the letter “a” if a loop is made on the last stroke. Conversely, the letter “e” in Sebivo does not look like the letters “us” in Sustiva which may help to differentiate the names (see below). However, there are several product characteristics which may increase the potential for confusion between the two names. Both Sustiva and Sebivo have overlapping characteristics such as dosage form (tablet), route of administration (oral), dose (600 mg), strength (600 mg), and frequency of administration (once daily). Thus, both products can be ordered as: 600 mg, 1 daily, #30. These shared product characteristics in conjunction with look-alike properties of the names may increase the potential for confusion. Additionally, the patient population and prescriber population may overlap since those infected with the HIV-1 virus may also be infected with the Hepatitis B virus. Orthographic similarities between the names coupled with overlapping product characteristics may increase the potential for confusion between the name pair.

*Sustiva 600mg  
1 po daily  
#30*

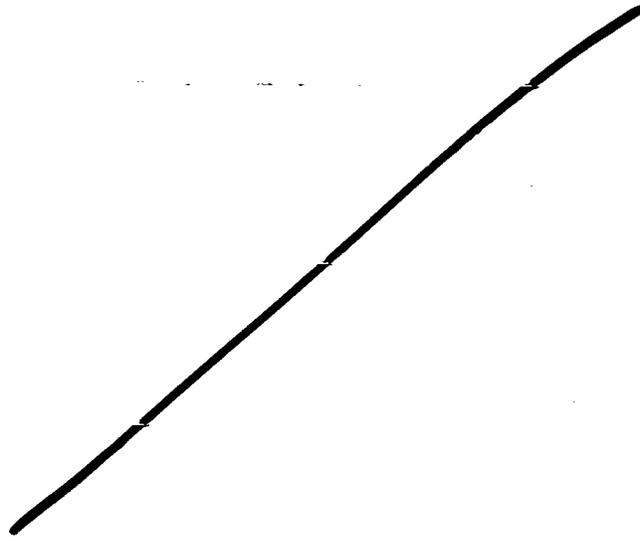
*Sebivo 600mg  
1 po daily  
#30*

- b. Stalevo was identified as a name that may sound like Sebivo when spoken. Stalevo is indicated for the treatment of Parkinson’s disease. The dose is individualized and the maximum recommended dose is 8 tablets per day with no more than 1 tablet taken at each dosing interval. Stalevo™ is available in three strengths: Stalevo 50 (carbidopa 12.5 mg/ levodopa 50 mg/entacapone 200 mg), Stalevo 100 (carbidopa 25 mg/levodopa 100 mg/entacapone 200 mg), and Stalevo 150 (carbidopa 37.5 mg/levodopa 150 mg/ entacapone 200 mg).

Stalevo and Sebivo may sound similar when the emphasis is placed on the second syllable of the names [Stalevo (STEH-LEE-VO) vs. Sebivo (SEH-'BEE-VO)]. Additionally, Stalevo and Sebivo each contain three syllables which contributes to the rhyming characteristic between the two names. Both products are available in an oral dosage form, however, there are no overlapping dosage strengths. Additionally, Stalevo is available in multiple strengths and has a strength modifier

as part of the name i.e. Stalevo 50. This may help to differentiate the products. For example, an order for Stalevo would have to specify the tablet strength since multiple strengths are available. Moreover, the dosing frequency differs for both drugs (once daily vs. multiple administration times per day). Despite some phonetic similarities, different product characteristics such as strength, dose, and dosing frequency may help to minimize the potential for confusion between Sebivo and Stalevo.

c.



d.



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

   § 552(b)(5) Deliberative Process

   § 552(b)(5) Draft Labeling

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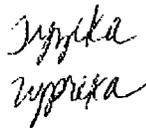
2. Look-alike/Sound-alike Confusion with Tyzeka

In reviewing the proprietary name Tyzeka, the primary concerns relating to look-alike and/or sound-alike confusion with Tyzeka are: Tiazac, Tyzine, Lyrica, and Zyprexa.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. Three respondents in the written inpatient prescription study misinterpreted the name as "Zyzeka" which looks similar to Zyprexa, a currently marketed U.S. drug product.

- a. Zyprexa was identified as a name with similar appearance to Tyzeka. Three participants in the inpatient prescription study misinterpreted the name as "Zyzeka" which looks similar to Zyprexa, a currently marketed U.S. product. Zyprexa contains olanzapine and is indicated for the treatment of schizophrenia and bipolar disorder. It is available in 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg strengths. Following are the recommended dosage regimens: schizophrenia, 5 mg to 10 mg once daily with titration up to 20 mg once daily if necessary; bipolar disorder, 10 mg or 15 mg once daily, initially, with titration up to a maximum of 20 mg once daily if necessary.

The first two letters of both names may look similar when written ("Ty" vs. "Zy"). Additionally, both names include a second downstroke ("z" and "p") in the third letter position of the name. However, Zyprexa contains an additional letter ("r") which may help to differentiate the names (see below).



Both products share some overlapping characteristics such as solid oral dosage form (tablets), route of administration (oral), and frequency of administration (once daily). However, they differ in product strength (600 mg vs. 2.5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg), and dose (600 mg once daily vs. 5 mg to 20 mg once daily). An order for Tyzeka may omit the strength but a strength for Zyprexa needs to be indicated on an order since it is available in multiple strengths. Although there are orthographic similarities between the names, the different product strengths may help to minimize the potential to confuse this name pair.

- b. Tiazac was identified as a name with phonetic similarities to Tyzeka. Tiazac contains diltiazem and is indicated for the treatment of hypertension and chronic stable angina. It is available in 120 mg, 180 mg, 240 mg, 360 mg, and 420 mg

strengths. The dose must be individualized. The recommended dose for hypertension is 120 mg to 240 mg once daily and may be increased to a maximum of 540 mg once daily. The recommended dose for chronic stable angina is 120 mg to 180 mg once daily, initially, and may be titrated up to a maximum of 540 mg per day.

The first syllable in each name may sound alike when spoken (“TY-” vs. “TI-”) and pronounced like (TĪE). Although both names contain a similar sounding syllable (ZĚK vs. ZĀC), these two syllables fall in a different place in the names (second syllable in Tyzeka vs. third syllable in Tiazac). Thus, the second syllable sound in Tiazac (“-A-”), pronounced like (“ĀH”), is different from the second syllable sound in Tyzeka (ZĚK) which helps to differentiate the names. Tiazac and Tyzeka have overlapping product characteristics such as the dosage form (tablet vs. capsule) and frequency of administration (once daily). However, there are no overlapping strengths or doses and this may help to differentiate the names. For example, a prescription for Tiazac would have to specify the strength to be dispensed since multiple strengths are available. Despite some phonetic similarities, the different product characteristics may help to minimize the potential to confuse Tyzeka with Tiazac.

- c. Tyzine was identified as a name with similar appearance to Tyzeka. Tyzine contains tetrahyralazine hydrochloride and is indicated for decongestion of nasal and nasopharyngeal mucosa. It is available in a 0.1% solution for adults and 0.05% solution for children 6 years of age and older. The recommended dose and frequency of administration for adults is 2 to 4 drops or 3 to 4 sprays in each nostril as needed but not more than every 3 hours. For children 6 years of age and older, the recommended dose and frequency of administration is 2 to 4 drops in each nostril as needed but not more than every 3 hours.

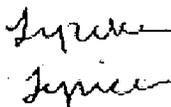
Both names begin with the same three letters “Tyz” which contributes to their look-alike similarity. Additionally, the letter “e” in Tyzeka and the letter “i” in Tyzine may look similar if the letter “i” is not prominently scripted or the dot is omitted. However, Tyzeka contains an upstroke characteristic with the letter “k” and this may help to distinguish the two names.

*Tyzine*  
*Tyzeka*

Additionally, Tyzeka and Tyzine have different product characteristics such as dosage form (tablet vs. solution), route of administration (oral vs. intranasal), strength (600 mg vs. 0.1% and 0.05%), and frequency of administration (once daily vs. every 3 hours as needed). Moreover, a prescription for Tyzine would have to specify the strength since multiple strengths are available. Despite the orthographic similarities, product characteristics may help to minimize the potential for confusion between the name pair.

- d. Lyrica was identified as a name with similar sound and appearance to Tyzeka. Lyrica contains pegalin and is indicated for the treatment of neuropathic pain, post-herpetic neuralgia, and epilepsy. Lyrica is available in eight strengths (see Table 2, page 5). Following are the recommended doses: neuropathic pain, 300 mg to 600 mg per day in three divided doses; post-herpetic neuralgia, 150 mg or 300 mg per day in three divided doses; and epilepsy, 150 mg to 600 mg per day in two or three divided doses.

The first two letters of both names (“Ly” vs. “Ty”) may look similar when written in cursive (see below). Additionally the letters “r” and “z” may look similar when written. However, the letter “k” in Tyzeka has an upstroke which may help to differentiate the names. The first and second syllables of both names may sound similar when pronounced in the following manner [ (LY-‘RĒ) vs. (‘TY-‘ZĒ)]. Additionally, the last syllable of both names sounds exactly alike (-CA vs. -KA) when pronounced like “KAH”. Both products have overlapping characteristics such as solid oral dosage form (tablet vs. capsule), total daily dose (600 mg), and route of administration (oral) which may contribute to confusion between the names. However, they differ in frequency of administration (once daily vs. two or three times per day) and strength (600 mg vs. 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg) which may help to differentiate the names. For example, a prescription for Lyrica would likely specify the frequency of administration as well as the strength since it can be given two or three times per day and there are multiple strengths available. Although there are some orthographic and phonetic similarities, different product characteristics may decrease the potential to confuse the name pair.



#### D. INDEPENDENT NAME ANALYSIS (Med-E.R.R.S.)

At the request of Idenix Pharmaceuticals and Novartis Pharma AG, Medical Error Recognition and Revision Strategies, Inc. (Med-E.R.R.S.), a subsidiary of the Institute for Safe Medication Practices (ISMP), conducted an independent analysis of the proposed proprietary name Sebivo. The “Sebivo Trademark Safety Evaluation for Idenix Pharmaceuticals and Novartis Pharma, AG” and “Tyzeka Trademark Safety Evaluation for Idenix Pharmaceuticals and Novartis Pharms, AG” reports were forwarded to DMETS by the Division of Anti-Viral Drug Products on August 23, 2005. Med-E.R.R.S. employed a total of 42 pharmacists for the study. Their responses are described below, along with the DMETS response.

##### SEBIVO

#### 1. Look-alike names with potential for confusion

Med-E.R.R.S. identified the name Selsun as being mentioned by respondents and evaluated by Med-E.R.R.S. staff as having potential for look-alike confusion when handwritten.

***DMETS Response:***

DMETS acknowledges the information presented by Med-E.R.R.S. Selsun was not identified by DMETS as having look-alike similarity to Sebivo. Selsun, selenium sulfide 2.5% shampoo, is indicated for the treatment of dandruff, seborrheic dermatitis, and tinea versicolor. The recommended initial frequency of use for dandruff/seborrheic dermatitis is twice weekly for two weeks; for tinea versicolor, the recommended frequency is once daily for 7 days. The letters “l” and “s” in Selsun may look like the letter “b” in Sebivo if the name is written in cursive and the letter “l” is placed very close to the letter “s”. However, the ending letters of each name look dissimilar (“un” vs. “ivo”). Because of the lack of convincing orthographic similarities between Sebivo and Selsun, and the product differences, DMETS feels there is minimal potential for confusion between these names.

2. Sound-alike names with potential for confusion

Med-E.R.R.S. found no significant sound-alike drug names with the potential for sound-alike confusion with Sebivo.

***DMETS Response:***

DMETS acknowledges the information presented by Med-E.R.R.S. However, see Section II of this review for sound-alike names identified by DMETS.

3. Medical terms with potential for confusion

Med-E.R.R.S. identified the medical terms “saliva” and “sebum” as being mentioned by respondents as having the potential for look-alike or sound-alike confusion with Sebivo™.

***DMETS Response:***

DMETS acknowledges the information presented by Med-E.R.R.S. “Saliva” is a salivary gland secretion and “sebum” is a sebaceous gland secretion. These are not names of medications and, therefore, the context in which they are likely to be used is different from the proprietary name, Sebivo. DMETS considers it unlikely that these medical terms will be confused with Sebivo.

4. Respondents’ suitability comments (rating) of proposed trademarks

Med-E.R.R.S. did not identify any pertinent comments from respondents regarding suitability of the proposed name, Sebivo

***DMETS Response:***

DMETS acknowledges the findings regarding the suitability of the name Sebivo. However, this has no bearing on potential sound-alike or look-alike names.

5. FDA and USAN Regulatory Assessment

Med-E.R.R.S. presented evaluation criteria drawn from the paper "Avoiding Trademark Trouble at FDA", that was published in the June 1996 issue of *Pharmaceutical Executive*.

***DMETS Response:***

DMETS cannot comment on the regulatory assessment provided by Med-E.R.R.S. The paper quoted was published in June 1996 and is not currently used by DMETS to evaluate tradenames.

6. Med-E.R.R.S. Overall Assessment of Name

Med-E.R.R.S. provided a cumulative appraisal of the proposed names by considering all the information collected in the evaluation process and applying it to a body of knowledge about medication error prevention to forecast the probability of errors with the proposed trademarks. Med-E.R.R.S. noted that the overall score for Sebivo was "4" and this was because of slight look-alike similarity with Selsun. Based on Med-E.R.R.S. analysis, a score of "4" indicates low vulnerability and they have determined that overall, the proposed trademark Sebivo has low vulnerability for look-alike and sound-alike confusion.

***DMETS Response:***

DMETS concurs with Med-E.R.R.S. that Selsun has low vulnerability for look-alike and sound-alike confusion with Sebivo. However, DMETS has identified the name, Sustiva, as having a high potential for confusion with Sebivo. [See Section II C1(a)].

**TYZEKA**

1. Look-alike names with potential for confusion

Med-E.R.R.S. identified Zyprexa as being mentioned by respondents and evaluated by Med-E.R.R.S. staff as having the having the potential for look-alike confusion when handwritten.

***DMETS Response:***

DMETS concurs with Med-E.R.R.S. that Tyzeka has the potential for look-alike confusion with Zyprexa. See Section II C2(a).

2. Sound-alike names with potential for confusion

Med-E.R.R.S. identified the names Zyprexa and Tiazac as being mentioned by respondents and evaluated by Med-E.R.R.S. staff as having potential for sound-alike confusion.

***DMETS Response:***

DMETS concurs with Med-E.R.R.S. that Tiazac has the potential for sound-alike confusion with Tyzeka. See Section II C(2b). Although Zyprexa was not identified by DMETS as having sound-alike confusion with Tyzeka, we identified Zyprexa to have look-alike similarity with Tyzeka. See Section II C2(a).

3. Medical terms with potential for confusion

Med-E.R.R.S. identified the medical terms “typhoid” and “tyzeria” as being mentioned by respondents as having the potential for look-alike or sound-alike confusion with Tyzeka.

***DMETS Response:***

DMETS acknowledges the information presented by Med-E.R.R.S. The word typhoid can be used as a noun referring to “typhoid fever” or “any of several diseases of domestic animals resembling human typhus or typhoid fever”; the word can also be used as an adjective meaning “of, relating to, or suggestive of typhus” or “of, relating to, affected with, or constituting typhoid fever”. This definition was obtained from the following website: ([www.nlm.nih.gov/medlineplus/plusdictionary.html](http://www.nlm.nih.gov/medlineplus/plusdictionary.html)). A online search through medical dictionaries did not produce a definition for “tyzeria”, however, the term “Tyzzeria” was found. “Tyzzeria is a genus of coccidian protozoa (suborder Eimeriina, order Eucoccidiida), characterized by the presence of oocysts containing eight naked sporozoites” ([http://www.mercksource.com/pp/us/cns/cns\\_home.jsp](http://www.mercksource.com/pp/us/cns/cns_home.jsp)). These are not names of medications and, therefore, the context in which they are likely to be used is different from the drug name Tyzeka. DMETS considers it unlikely that these medical terms will be confused with Tyzeka.

4. Respondents’ suitability comments (rating) of proposed trademarks

Med-E.R.R.S. did not identify any pertinent comments from respondents regarding suitability of the proposed name, Tyzeka.

***DMETS Response:***

DMETS acknowledges the findings regarding the suitability of the name Tyzeka. However, this has no bearing on potential sound-alike or look-alike names.

5. FDA and USAN Regulatory Assessment

Med-E.R.R.S. presented evaluation criteria drawn from the paper “Avoiding Trademark Trouble at FDA”, that was published in the June 1996 issue of *Pharmaceutical Executive*.

***DMETS Response:***

DMETS cannot comment on the regulatory assessment provided by Med-E.R.R.S. The paper quoted was published in June 1996 and is not currently used by DMETS to evaluate tradenames.

6. Med-E.R.R.S. Overall Assessment of Name

Med-E.R.R.S. provided a cumulative appraisal of the proposed names by considering all the information collected in the evaluation process and applying it to a body of knowledge about medication error prevention to forecast the probability of errors with the proposed trademarks. Med-E.R.R.S. noted that the overall score for Tyzeka was "3" and this was because of look-alike and sound-alike similarity with Zyprexa and slight sound-alike similarity with Tiazac. A score of "3" indicates moderate vulnerability.

**DMETS Response:**

DMETS believes the differences in strength between Tyzeka and Zyprexa or Tiazac will minimize the potential for confusion.

**III. COMMENTS TO THE SPONSOR:**

DMETS does not recommend the use of the proprietary name, Sebivo. In reviewing the proprietary names, the primary concerns related to look-alike and/or sound-alike confusion with Sustiva. DMETS has no objections to the use of the proprietary name, Tyzeka.

Sustiva was identified as having orthographic similarity with Sebivo. Additionally, one respondent in the inpatient prescription study misinterpreted the name Sebivo as Sustiva. Sustiva is an antiretroviral agent indicated for the treatment of HIV infection. The recommended adult dose is 600 mg once daily in combination with other antiretroviral agents.

Both names begin with the letter "S". Additionally, Sustiva contains the upstroke letter "t" which can look like the upstroke letter "b" in Sebivo when the letter "t" is not crossed. The last three letters of both names may also look similar ("ivo" vs. "iva"). Furthermore, the letter "o" may look like the letter "a" if a loop is made on the last stroke. Conversely, the letter "e" in Sebivo does not look like the letters "us" in Sustiva which may help to differentiate the names (see below). However, there are several product characteristics which may increase the potential for confusion between the two names. Both Sustiva and Sebivo have overlapping characteristics such as dosage form (tablet), route of administration (oral), dose (600 mg), strength (600 mg), and frequency of administration (once daily). Thus, both products can be ordered as: 600 mg, 1 daily, #30. These shared product characteristics in conjunction with look-alike properties of the names may increase the potential for confusion. Additionally, the patient population and prescriber population may overlap since those infected with the HIV-1 virus may also be infected with the Hepatitis B virus. Orthographic similarities between the names coupled with overlapping product characteristics may increase the potential for confusion between the name pair.

*Sustiva 600mg  
i po daily  
#30*

*Sebivo 600mg  
i po daily  
#30*

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified several areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABEL

Increase the prominence of the established name.

2. INSERT LABELING

- a. The abbreviations “ $\mu\text{M}$ ” and “ $\mu\text{g}$ ” are used in the insert labeling. The abbreviation “ $\mu$ ” may be mistaken for the letter “m” and be misinterpreted as meaning “milli”, thus leading to misinterpretations of the information presented. This abbreviation appears on the Institute for Safe Medication Practices (ISMP) list of dangerous abbreviations. In June 2006, the FDA and the ISMP launched a nationwide health professional education campaign aimed at reducing the number of common but preventable sources of medication mix-ups and mistakes caused by the use of unclear medical abbreviations. Thus we request that OND and pharmaceutical companies not approve or use abbreviations in the labels and labeling as they can be misinterpreted and contribute to errors. DMETS recommends writing out the abbreviations or revise to read “mcg” rather than “ $\mu\text{g}$ ”.
- b. In the PRECAUTIONS section under Information for Patients, it states that a patient package insert (PPI) is available. This was not submitted for review and comment. DMETS recommends that DMETS and the Division of Surveillance, Research, and Communication Support (DSRCS) be contacted for a separate review of the PPI when it becomes available.

**Appendix A. DMETS Prescription Study Results for Sebivo™**

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<b>Inpatient</b>	<b>Outpatient</b>	<b>Verbal</b>
Scbiro	Gebivo	Cebivo
Scbivo	Gebivo	Cyvio
Schivo	Gebivo	Deprivo
Schkivo	Gebivo	Gebivo
Schuiro	Gobivo	Livido
Sebivo	Sebivo	Sadivo
Sebivo	Sebivo	Schivo
Sebivo	Sebivo	Sebevo
Sebivo	Sebivo	Sebevo
Sebivo	Sebivo	Sebivo
Sekivo	Sebivo	Sepivo
Sekivo	Sebivo	
Selvivo	Sebivo	
Sibiro	Sebivo	
Sulmizo	Sebivo	
Sustiva	Sebivo	
	Sebivo	

**Appendix A. DMETS Prescription Study Results for Tyzeka™**

<b>Inpatient</b>	<b>Outpatient</b>	<b>Verbal</b>
lyzeka	Tyzeba	Kaizeeka
Jyzeka	Tyzeba	Kyzica
Jyzeka	Tyzeba	Tizeca
Lyzeka	Tyzeba	Tizecose
Qyzeka	Tyzeba	Tizeka
Tizeka	Tyzeba	Tizica
Tyzeka	Tyzeba	Tyzeca
Tyzeka	Tyzeba	Tyzeco
Tyzeka	Tyzeda	Tyzeka
Tyzeka	Tyzeda	Tyzica
Tyzeka	Tyzeda	Tyzica
Tyzeka	Tyzeka	Tyzica
Tyzeka	Tyzeka	
Tyzeka (lyzeka)	Tyzeke	
Tyzexa		
Zyzeka		
Zyzeka		
Zyzeka		

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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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Loretta Holmes  
8/15/2006 04:20:08 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
8/15/2006 04:24:31 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
8/15/2006 04:34:48 PM  
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 60,459

Idenix Pharmaceuticals  
Attention: David Hallinan, Ph.D.  
Vice President Regulatory Affairs  
60 Hampshire Street  
Cambridge, MA 02139

Dear Dr. Hallinan:

Please refer to the meeting between representatives of your firm and FDA on April 5, 2005. The purpose of the Pre-NDA meeting was to discuss the format and content of the planned NDA for LdT (telbivudine).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeff O'Neill, ACRN, Regulatory Health Project Manager, at 301-827-2362.

Sincerely,

*{See appended electronic signature page}*

Deb Birnkrant, MD  
Division Director  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Enclosure

## RECORD OF INDUSTRY MEETING

**Date:** April 5, 2005

**IND:** 60,459

**Sponsor:** Idenix Pharmaceuticals  
60 Hampshire Street  
Cambridge, MA 02139

**Drug:** LdT (telbivudine)

**Indication:** Treatment of chronic Hepatitis B

**FDA Attendees:** Mark Goldberger, M.D., M.P.H., Director, Office of Drug Evaluation IV (ODEIV)  
Edward Cox, M.D., Deputy Director, ODEIV  
Debra Birnkrant, M.D., Director, Division of Antiviral Drug Products (DAVDP)  
Jeffrey S. Murray, M.D., M.P.H., Deputy Division Director, DAVDP  
Katherine A. Laessig, M.D., Medical Team Leader, DAVDP  
Yoshihiko Murata, M.D., Ph.D., Medical Officer, DAVDP  
Ita Yuen, Ph.D., Pharmacologist, DAVDP  
Kellie S. Reynolds, Pharm.D., Clinical Pharmacology Team Leader, DAVDP  
Jenny H. Zheng, Ph.D., Clinical Pharmacologist, DAVDP  
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVDP  
Sung Rhee, Ph.D., Microbiologist, DAVDP  
Greg Soon, Ph.D., Statistical Team Leader, DAVDP  
Fraser Smith, Ph.D., Statistician, DAVDP  
David Roeder, Assoc. Director, Regulatory Affairs, ODEIV  
Virginia Behr, Chief, Project Management Staff, DAVDP  
Monica Zeballos, Pharm.D., Regulatory Project Manager, DAVDP  
Kenneth Shade, R.N., J.D., Regulatory Project Manager, DAVDP  
Gary Gensinger, Director, Review Technology Staff, OIT  
Fran Weiss, Regulatory Information Specialist, Review Technology Staff, OIT  
Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVDP

**Idenix Attendees:** David Hallinan, Ph.D., Vice President, Regulatory Affairs  
Rumana Rahman, Director, Regulatory Affairs  
Nathaniel Brown, M.D., Chief Medical Officer and Executive V.P., Clinical Development  
Dereck Tait, M.D., Vice President, Clinical Research  
George Chao, Ph.D., Vice President, Biostatistics & Data Management  
Jim McDougall, Ph.D., Director, Biostatistics  
Barbara Fielman, Associate Director, Clinical Operations  
Xiao Jian Zhou, Ph.D., Clinical Pharmacology  
David Standring, Ph.D., Vice President, Biology  
David Shlaes, M.D., Ph.D., Research and Development  
Edward Bridges, Ph.D., Senior Director, Pharmacology and Toxicology

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**Novartis Attendees:** George Harb, M.D., M.P.H., Director, Infectious and Tropical Diseases  
Michael Buska, Director, Regulatory Affairs  
June Ke, Ph.D., Senior Lead Pharmacokineticist  
Elizabeth Olek, D.O., M.P.H., R.P.H., Clinical Research Physician  
Eric Floyd, Vice President, Global Regulatory Affairs  
Weibin Bao, Senior Principle Statistician

**Subject:** Pre-NDA Industry Meeting

**Background:**

The IND for telbivudine (LdT) went into effect on July 1, 2000. An End of Phase Two (EOP2) meeting with the Division was held June 17, 2002, and an EOP2 meeting to discuss outstanding chemistry and manufacturing issues was held November 13, 2002. A request for a Pre-NDA meeting was received on January 31, 2005 followed by the background document received March 4, 2005. This Pre-NDA meeting was held to discuss the format and content of the Sponsor's planned NDA submission targeted for submission in December 2005.

**Discussion:**

The background document contained regulatory, clinical, and non-clinical questions for discussion. After a short presentation by the Sponsor, the questions were discussed in the order listed below. The Sponsor's questions and comments are in normal type and the Division of Antiviral Drug Product's comments are in italics.

**Clinical**

- 1.a. At the time of NDA submission, the telbivudine safety database is expected to contain in excess of 1,500 human subjects and patients, with approximately 700 hepatitis B patients treated at the recommended dose of 600 mg QD for 12 months and approximately 1,100 patients for six months. The size of this safety database, as well as the duration of exposure, will be larger than that recommended in the ICH E1 exposure guideline and is adequate to support the safety of telbivudine at the time of initial registration. Does the Division agree?

*The Division agreed that given the information in the Pre-NDA submission, the size of the safety database, and the duration of exposure to telbivudine, this will likely support the safety of telbivudine at the time of initial NDA submission. In addition, the Division requested that summaries of any available six-month data from 1,100 patients described in the Pre-NDA package (Table 5-6, p. 47) be included in the ISS of the NDA.*

- 1.b. Plan for abbreviated safety reports (SAEs, deaths, discontinuations due to AEs and grade 3/4 laboratory abnormalities) for ongoing studies – does the Division concur?

*The Division requested that the safety data from ongoing studies be included in the ISS. Once these studies are completed, the respective study reports should be submitted to the Division.*

- 1.c. For long term studies ( $\geq 12$  months; studies 003, 007, and 010), datasets will be provided per the 1999 electronic submission guidance with a standardized format across studies. Does the Division concur with this proposed plan?

*The Division agreed with the proposed plan to submit electronic datasets per the 1999 electronic submission guidance.*

- 2.a. The pivotal Phase III study (Study NV-02B-007 consists of HBeAg-positive and HBeAg-negative patients).

According to previous Agency agreement, the statistically significant level within each subpopulation analysis of the primary endpoint and the key secondary endpoint (Histologic response) will be at 0.0432. If both reach statistical significance, no further analysis is required. If not, and there is no interaction between treatment and subpopulation, the two subpopulations can be pooled with an overall significance level at 0.000933. Is this acceptable to the Division?

- 2b. We plan to use the order of the secondary variables specified in Section 5.2.7.1 for sequential testing to protect the overall Type I error. We will further specify the non-inferiority (NI) criteria for these secondary efficacy variables in the Statistical Analysis Plan. If the statistical significance criteria for the secondary efficacy variables for NI claim are met consecutively from the top of the list, then claims for these secondary efficacy parameters may be included in the proposed product label. Is this acceptable to the Division?

- 2d. The paired liver biopsy slides from the 007 study patients will be masked for patient identifiers, treatment assignment, date, and sequence (baseline/post treatment). These slides will be read and scored by \_\_\_\_\_, an experienced histopathologist who is well-known to the Agency from his previous hepatitis trial work in multiple drug development programs. Since histology is not a primary endpoint in the 007 trial, but a key secondary endpoint, we propose to use an independent CRO for histology data QA. This CRO will not have access to the randomization schedule. The histology database is expected to be locked and delivered to Idenix at the end of July 2005. The clinical database however, will be locked and delivered to Idenix from the Clinical CRO \_\_\_\_\_ in June 2005. We plan to unblind the clinical database as soon as the CRF and laboratory data are locked for the analysis, to begin preparation of the clinical study report. Subsequently (about one month later), the locked histology database will be delivered by the CRO and integrated with the clinical database; then the histologic analyses can be incorporated into the study report. This approach will be prospectively defined in the statistical analysis plan for this study. Is this acceptable to the Division?

*In regards to questions 2a, 2b, and 2d, the Division referred to their facsimile containing statistical comments dated 4/1/05.*

*The Division asked why some of the secondary variables in their slide for 2b appear to be different from the ones in Section 5.2.7.1 of the background document.*

The Sponsor stated that the list of secondary variables on their slide will take precedence over the list in the background document and that endpoints 6, 7, and 8 on their slides (Virologic Response, HBeAg Serocon and HBeAg Loss) are only applicable to HBeAg+ patients.

The Sponsor would like to test the other secondary endpoints within HBeAg+ and HBeAg- patients separately at the 0.05 level of significance. The last two endpoints on slides 9 and 10 (HBsAg Loss and HBsAg Serocon) are expected to have low incidence. Because of the anticipated low power for the last two endpoints, the Sponsor would like to perform these hypothesis tests using the 0.05 level of significance.

In addition, they will submit a statistical plan (SAP) within 4-6 weeks with more details. The order of the secondary efficacy parameters in the SAP will supersede the order presented in the slide.

*The Division advised the Sponsor to make sure that there are no treatment by HBeAg subgroup interactions.*

*The Division added that in case results for the ordered secondary hypotheses are negative, failure to demonstrate non-inferiority should also go into the label. If the confidence intervals are small and telbivudine is non-inferior but also inferior to (significantly worse than) lamivudine this should also go in the label.*

In response to comments from the from the 4/1/05 facsimile, in reference to question 2d where the Division asked for the name of the CRO, the Sponsor stated that they could use [REDACTED] or another CRO that is in the [REDACTED] area.

*The Division expressed concerns that the same CRO would be performing the unblinded analysis of the clinical data [REDACTED] and the subsequent analysis of the histology data [REDACTED]*

In response to the Division's concerns, the Sponsor referenced their slide outlining their plans for the pivotal study unblinding process:

- The independent blinded CRO will convert Excel to SAS database, and perform QC and query resolution versus source documents from [REDACTED]. The CRO will have no access to the treatment codes.
- No 007 study results or patient treatment identification will be provided to [REDACTED] his staff, or the independent CRO prior to the final locked Histology database being provided to Idenix.
- Only the final locked Histology database will be delivered to Idenix, no intermediate Histology databases.
- This approach will be prospectively defined in the statistical analysis plan.

The Sponsor also stated that given the Division's concerns, they would seriously consider using the CRO in the [REDACTED] area.

2.c. Is the proposed listing of statistical tables and sample shell tables for key safety and efficacy data variables for pivotal study NV-02B-007 acceptable?

*The Division requested that the following additional analyses/table be included in the NDA. This request was included in faxed comments to the Sponsor on April 11, 2005:*

- *Efficacy/Safety analyses with respect to demographic characteristics (gender, age, racial subgroups)*
- *Laboratory analyses: Marked outliers and study drug discontinuation due to laboratory abnormalities; Grade shift tables for laboratory values, i.e. from normal to abnormal; and comparison of mean/median changes from baseline across treatment groups. We recognize that the safety analyses are ongoing and marked outliers for laboratory parameters may be more specifically defined (e.g. by standard deviation cut-offs or by specific lower/upper bounds) at a later date.*
- *Listings of AEs that caused treatment dose-reduction or interruptions.*

2.e. We plan to submit a comprehensive summary of any treatment-emergent HBV viral resistance from our Phase II and Phase III clinical trials in the NDA, and the impact of viral resistance on key efficacy parameters within the Efficacy data included in module 5 and (in briefer form) in module 2 of the CTD submission. We would appreciate the Division's suggestions regarding placement of such resistance data in the CTD format.

*Regarding the location of microbiology information including resistance data in the CTD format, the Division stated that the Microbiology summary should be in Module 2 and the comprehensive microbiology information in Module 5, Section 5.3.5.4., called "Other Studies". The outline for the Microbiology study reports and data were included in the April 11, 2005 facsimile.*

*In addition to the resistant data summary, the Division stated that they expect to receive the resistance data in the HBV resistance template format and recommended that the Sponsor presubmit the first data set when it is available. The latest version of the HBV resistance template was emailed to the Sponsor on April 11, 2005.*

### **3. Phase III – NV-02B-011 (decompensated patient population)**

Per previous requests by the Agency, we plan to submit blinded preliminary data (70 or more patients, with 6 months data on 50 patients) from the ongoing NV-02B-011 study in patients with decompensated liver disease, to support a priority review assessment for the NDA.

Does the FDA prefer the submission of pooled blinded summary safety and efficacy data or accept the submission of unblinded summary data from our DSMB independent biostatistician bypassing any review from Sponsor?

*The Division stated that we would like to see the data unblinded by treatment group and would not want Idenix to see this unblinded data.*

The Sponsor stated that they will only see pooled data and DAVDP can directly contact their lead statistician.

*It was agreed that further discussion regarding how to handle sharing the unblinded data would be necessary.*

#### 4. Clinical Pharmacology

Protocol NV-02B-006 evaluated the impact of varying degrees of renal impairment on telbivudine PK. [REDACTED] Based on the results of this 006 study, a [REDACTED], a dose interval adjustment will be proposed: e.g. 600 mg every 48 hours (CrCL 30-49 mL/min) or every 72 hours (CrCL <30 mL/min or ESRD). Refer to Appendix 4, Section 1.1.5, summary of results from study NV-02B-006 for supportive information. Does the Division concur with this approach?

*The Division stated that this would be a review issue. It can not be determined at this time if this approach is acceptable. The Division asked if any PK/PD data are available to justify the increased Cmax or if any study to look at this is planned?*

The Sponsor stated that they do not have direct PK/PD data from Study 006 but would see if they could do additional PK/PD studies.

*The Division requested that the Sponsor submit with the NDA submission the following information for any PK/PD analyses that are conducted:*

- *All raw data that were used for population PK/PD analyses. Please include the following variables in the PD database: ID, treatment, time relative to the start of treatment, viral load, IC50 in vitro, AUC, Ctrough, CD4 cell counts. You may include other relevant variables in the PD database. The data should be submitted as SAS transport files.*
- *Data files (SAS transport files) used for base model and final model.*
- *Databases that were generated for simulation.*
- *Model and output files. All model files should be submitted as "txt" files. For example filename "test1.ctl" should be renamed as "test1\_ctl.txt".*

[REDACTED]

The Sponsor stated that they plan to

[REDACTED]

#### Preclinical

1. Repeated dose toxicology studies along with a cardiovascular safety pharmacology study in monkeys were conducted. Does the Division concur that these studies together with the hERG assay support the preclinical evaluation of cardiac safety?

*The Division concurred.*

2. Does the Division concur that the Safety Pharmacology program evaluating cardiovascular, respiratory, and CNS function supports the registration of telbivudine?

*The Division concurred.*

3. The submission will contain a standard 104 week carcinogenicity study in rats in addition to a 26 week carcinogenicity study in transgenic mice. Does the Division concur that the inclusion of these two study reports fulfills previous agreements between the Sponsor and the Agency, and meets the requirements for evaluation of the carcinogenic potential of telbivudine?

*The Division concurred and requested submission of completed carcinogenicity reports to the IND prior to the initial NDA submission.*

4. Idenix is conducting nonclinical toxicology studies with telbivudine and valtorcitabine (LdC, IND 64,704) to support the development of a fixed dose combination of telbivudine and valtorcitabine for the treatment of chronic hepatitis B patients who are suboptimally suppressed on current treatment. Idenix requests a waiver for submission of these study reports in the telbivudine submission that are not relevant for the preclinical evaluation of telbivudine alone for the intended indication. Does the Division concur?

*The Division concurred.*

### **Regulatory**

1. Idenix proposes to submit the telbivudine NDA utilizing the eCTD format specified per ICH (M4 guidance; September 2002 and annex January 2004) that will serve as the archival and review copy. The electronic submission will follow the FDA August 2003 Draft Guidance "Providing regulatory submissions in electronic format - Human Pharmaceutical Product Application and Related Submissions" and the October 2003 Draft Guidance, "Providing Regulatory Submissions in Electronic Format- General Considerations", utilizing the file formats (PDF/SAS) specified in this guidance. Does the Division concur with the proposed format for the telbivudine NDA?

*The Division referred to their facsimile dated April 1, 2005 which stated that the Division agrees that we would like to have an electronic submission of the telbivudine NDA and will need SAS programs in pdf and text formats and SAS datasets submitted as SAS transport files.*

*In addition, in advance of the anticipated NDA submission, the Division encouraged the submission of representative safety and efficacy datasets, e.g. from the Phase 2B study 003, so that the review team may determine the accessibility of the data via the eCTD format.*

2. Does the Division concur with the proposed location of Microbiology information in the NDA (CTD Sections 2.6.2.2, Primary Pharmacodynamics and Section 2.7.3, Clinical Pharmacology)?

*The Division stated that they will provide specific recommendations regarding the Microbiology section.*

3. Idenix has evaluated the information required to be included in the CTD Clinical Summary, Module 2 Sections 2.7.3 and 2.7.4 (Overview of Efficacy and Overview of Safety, respectively).

Efficacy and safety data will be primarily derived from a single large Phase III pivotal study (NV-02B-007), in which more than 680 patients will be treated with telbivudine for one year. Other non-pivotal, supportive studies of different treatment durations will contribute to the total safety database.

Therefore, based on the studies that are planned for inclusion in the NDA, Idenix proposes that the clinical information included in module 2.7.3 and 2.7.4 of the CTD essentially reflect the integrated safety and efficacy data, and that preparation of separate ISS and/or ISE sections would not aid the medical reviewer of this NDA. Does the Division concur? (Also refer to Section 5.2.6.3)

*The Division requested that Idenix submit ISS and ISE, particularly to summarize key safety data (e.g. AEs, SAEs, deaths) from ongoing and completed studies. Given our additional requests for data to be included in the NDA, please provide additional details on the proposed contents of the ISS and ISE.*

*In addition, the Division asked for additional details on the proposed study of telbivudine in treatment-naïve, HIV-HBV co-infected patients in Thailand.*

4. Based on data demonstrating that telbivudine has improved clinical efficacy and/or an improved safety profile over other approved antiviral agents for the treatment of chronic hepatitis B, does the Division agree that a Priority Review may be granted for this NDA? Can the Division comment on the current relevance of previously discussed and agreed upon criteria for a Priority Review designation, confirming the requirements for such a designation? (Refer to Section 3.2.1.4 for further details of previous discussions)

*The Division stated that consistent with previous discussions between the Division and Idenix, whether or not the anticipated NDA for telbivudine will merit a Priority Review will be determined upon review of the available data at the time of NDA submission. As was previously discussed, consideration of the NDA for a Priority Review will likely require safety and efficacy data **in addition** to the preliminary data from the 011 study at the time of filing.*

5. Idenix proposes, per 21 CFR 314.50, to submit Case Report Forms (CRFs) only for those subjects/patients who died on study or discontinued due to adverse events. Is this acceptable to the Division?

*Based on the information in the pre-NDA submission, the Division requested that CRFs from deaths, treatment discontinuation, and HBV flares be submitted in the initial NDA. In addition, we requested the submission of CRFs from a representative set of SAEs (by geographic region of the study sites and/or by specific classes of SAEs as determined by the initial safety analysis by Idenix). Lastly, we requested that a listing of all SAEs be submitted in the NDA such that CRFs from specific SAEs of interest may be requested during the NDA review process.*

6. As previously discussed with DAVDP, we are developing a pediatric plan to include longer-term treatment of this patient population, and thus will not have data by NDA submission time. Does the Division concur that a pediatric deferral can be granted for the pediatric population for the initial telbivudine NDA submission?

*The Division stated that carcinogenicity study reports are of interest with regard to pediatric drug development and should be submitted to the IND prior to the planned submission of this NDA. The Division added that additional information on the pivotal bioequivalence study for 1 [REDACTED] [REDACTED] under development is needed for use of telbivudine in the pediatric population. Assuming that no outstanding issues remain with regard to carcinogenicity [REDACTED] bioequivalence, pediatric deferral may be considered at the time of the NDA submission.*

**Action Items**

- Division will send a facsimile with additional comments from the review team.
- Division will send the outline for the microbiology section of the NDA.
- Division will provide the Sponsor with the Resistance Template.
- Idenix will submit a SAP plan.
- Idenix will submit safety data from ongoing studies in the ISS and completed studies will be submitted with their respective study reports.
- Idenix will submit completed carcinogenicity reports to the IND prior to the initial NDA submission.

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this page is the manifestation of the electronic signature.**  
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/s/

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Debra Birnkrant  
5/6/05 02:59:54 PM  
IND 60,459



Food and Drug Administration  
Division of Antiviral Products  
Office of Antimicrobial Products  
Silver Spring, MD 20903

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011/SN-005  
**Drug:** SEBIVO™ (telbivudine)  
**Date:** March 31, 2006  
**To:** David Hallinan, PhD  
**Sponsor:** Idenix Pharmaceuticals, Inc.  
**From:** Kenny Shade, JD, BSN  
**Through:** Charlene Brown, MD, Clinical Reviewer  
**Concur:** Katherine Laessig, MD, Clinical Team Leader  
**Subject:** Clinical Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011/SN-005 for Sebivo™ submitted February 21, 2006.

**Clinical Comments**

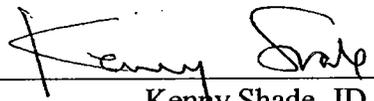
1. Please clarify where laboratory data used to determine the primary efficacy endpoint of therapeutic response at Week 52 were sent to be analyzed.
2. Please clarify whether or not corresponding copies of the source documents containing the results of the laboratory tests for serum HBV DNA suppression, HBeAg loss and ALT normalization have been provided to the clinical investigator sites for NV-02B-007.
3. Please provide narratives for all subjects who developed Grade 3 or Grade 4 CK elevations during studies NV-02B-007, NV-02B-003, and NV-02B-015. Please include discussion of any musculoskeletal complaints that these subjects may have experienced. Also, please provide a key or guide to these narratives.
4. Please provide narratives for all subjects in NV-02B-007, NV-02B-003, and NV-02B-015 that developed neuropathic or other sensory adverse events including dysethesia, sensory loss, neuropathic pain, polyneuropathy, sciatica, paresthesia, hypoesthesia, and neuralgia.
5. Please ensure that narratives include time course for the event and study drug intake, trajectory of relevant laboratory results before, after and during the event, relevant concomitant medications and illnesses, investigations, interventions and/or treatments,

outcomes, temporary or permanent study drug discontinuations, and reasons for possible relatedness or unrelatedness to study drug.

6. The urinalysis results provided in individual listings dataset Labs8 for NV-02B-007 include pH, specific gravity, protein and glucose. Do you have data on whether or not the urinalyses were found to be heme positive and/or whether or not red blood cells were present? If so, please provide this data for all subjects who developed Grade 3 or Grade 4 CK elevations.
7. As part of the safety evaluations for grade 3 or 4 laboratory events that occurred in more than 5% of patients in the telbivudine group, the laboratory endpoint was to be analyzed to determine if there is a correlation between the grade 3/4 laboratory values and the baseline covariates of age, BMI, ethnicity, geographic region, HBV genotype, years since diagnosis, presence of cirrhosis, prior interferon therapy, probable transmission route, HBV DNA tertile level, and Knodell HAI score. More than 5% of patients in the telbivudine group experienced grade 3 and 4 (combined) CK values. If this analysis was completed for subjects with grade 3 and 4 CK results, please identify the relevant dataset as well as the sections in the submission where the results of this analysis are discussed. If this analysis was not completed, please complete it and submit the relevant dataset, results and discussion.
8. Please create a separate individual listings datasets for subjects in NV-02B-007 with CK elevations of any grade at any time, including up to 30 days after completing study drug:
  - o Dataset for CK elevations
    - Protocol
    - USUBJID
    - STRATE
    - RX (treatment group)
    - Age
    - Race
    - Gender
    - Height
    - Weight
    - Visit
    - Testdesc, results, normal high, normal low, and baseline values for the following:
      - Creatine Kinase
      - Creatinine
      - Urinalysis (only if you have heme results)
    - Toxicity Grade
    - Outcome\_
    - Relat\_ (relatedness to study drug)
    - Trtmnt\_ (whether or not treatment was required)
    - On Treatment (from Baseline to the date of last treatment **plus 30 days**, and from restarting blinded study medication to **30 days** after the date of last treatment)
    - Action (taken with study drug)
    - Study Day of Lab Collection
    - Study Day of Resolution

9. Please create a separate individual listings datasets for all subjects in NV-02B-007 with ALT elevations of any grade and include the following variables:
  - Dataset for Liver Function elevations
    - Protocol
    - USUBJID
    - RX (treatment group)
    - Age
    - Race
    - Gender
    - Visit
    - Testdesc, results, normal hi, normal low, and baseline values for the following
      - ALT
      - AST
      - Total Bilrubin
      - Amylase
      - Lipase
    - Toxicity Grade
    - Outcome\_
    - Relat\_ (relatedness to study drug)
    - Trtmnt\_ (whether or not treatment was required)
    - On Treatment (from Baseline to the date of last treatment **plus 30 days**, and from restarting blinded study medication to **30 days** after the date of last treatment)
    - Action (taken with study drug)
    - Study Day of Lab Collection
    - Study Day of Resolution
10. For both datasets, please exclude all subjects who did not presumptively receive at least one dose of the study medication with at least one observation after Baseline.
11. If there are difficulties with creating the datasets described above, please notify Mr. Shade and we can explore possible modifications.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

  
Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
3/31/2006 10:28:01 AM  
CSO

Kathrine Laessig  
3/31/2006 11:24:02 AM  
MEDICAL OFFICER

## REQUEST FOR CONSULTATION

To (Division/Office):

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
WO22, RM 4447**

FROM: Kenny Shade  
Regulatory Health Project Manager  
DAVP, HFD-530 WO BLDG 22, Room 6319

DATE March 23, 2006	IND NO.	NDA NO. 22-011	TYPE OF DOCUMENT Trade Name Review Request	DATE OF DOCUMENT March 23, 2006
NAME OF DRUG Sebivo		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG Antiviral/Systemic/Hepati tis/7030170	DESIRED COMPLETION DATE July 2006

NAME OF FIRM: Idenix Pharmaceuticals, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
|--|--|--|

#### II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

#### IV. DRUG EXPERIENCE

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: A consult was submitted in August, 2005 for this trade name while in IND (60,459) phase of development and was reviewed and tentatively approved. The sponsor has since submitted a NDA for this drug on December 30, 2005.

PDUFA DATE: October 2, 2006  
 ATTACHMENTS: Draft Package Insert, Container and Carton Labels  
 CC: Archival IND/NDA Reference IND 60,459/ NDA 22-011  
 HFD-530/Division File  
 HFD-530/RPM  
 HFD-530/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER Kenny Shade 301-796-0807	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

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Kenny Shade  
3/23/2006 09:59:52 AM



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011  
**Drug:** SEBIVO™ (telbivudine)  
**Date:** March 15, 2006  
**To:** David Hallinan, Ph.D.  
**Sponsor:** Idenix Pharmaceuticals, Inc.  
**From:** Kenny Shade, JD, BSN  
**Through:** Charlene Brown, M.D., Clinical Reviewer  
**Concur:** Katherine Laessig, MD, Clinical Team Leader  
**Subject:** Clinical Comments

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The following comments related to the clinical datasets submitted for Protocol NV-02B-007 are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for Sebivo™ submitted December 30, 2005.

**Clinical Comments**

1. The variables DLDDT, Date of Last Dose (derived) and DLDDTSD, Study Day of DLDDT in your "Drug Dispensation" Individual Subject Listings Datasets is missing data for most of the study subjects. Is this because most of the subjects are still on study drug? Please clarify.
2. In the AE Individual Subject Listings Dataset, there are several rows which include patient information (ID, RX, age, gender, race, baseline date, stratification), but do not have any AE data (e.g. event, preferred term, soc, onset date, resolution date, etc), despite a Yes value for the AEYN variable. Please explain.
3. Also in the AE Individual Subject Listings Dataset, there is missing data for many subjects for the variables RESOLVDT and RESOLVSD, when ONSETDT and ONSETSD are provided. Does this mean that the AE had not resolved by the dataset lock date? Please clarify.
4. Please provide an abbreviated key or guide for the Case Report Forms (CRFs) that includes the reason the study, site, patient ID and the reason that a CRF is being provided for the patient.

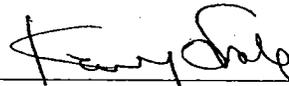
March 15 2006

5. The analysis A\_AE datasets submitted use a Y/N variable to assess whether or not an AE occurred on treatment. Your definition of "on treatment" for this purpose is defined as an AE occurring during treatment or up to 7 days after the last dose of treatment. The Division of Antiviral Products usually considers an AE to have occurred "on treatment" if it occurs while taking the study drug or up to 30 days after the last treatment dose.
6. There are 25 adverse events for which the information regarding timing of either the onset of the adverse event (ONSETDSD or ONSETDT) or the resolution of the adverse event (RESOLVSD and RESOLVDT) or both are not provided. Although the Day of the Last Dose of Study Drug (DLDDTSD) is available is provided for the subjects with these AEs, it is still not possible to determine whether or not these AEs occurred on treatment without knowing the AE onset. Also, if the resolution date is not provided or occurs after the last dose of study drug, it is not possible to assess whether or not the AE occurred on treatment unless the AE onset is provided. Please provide this information for the following USUBJID/EVENT combinations from the AE dataset for Protocol NV-02B-007:

007-008-036	RIGHT UPPER QUADRANT PAIN
007-008-036	ARRHYTHMIA
007-008-036	FINGER JOINT PAIN
007-008-036	LEFT KNEE JOINT PAIN
007-008-036	LEFT SHOULDER PAIN
007-008-036	LOWER BACK PAIN
007-012-001	ABDOMINAL MUSCLE CRAMP
007-012-001	WEIGHT LOSS
007-012-015	CONSTIPATION
007-012-015	NUMBNESS AT FINGERTIP.
007-012-015	UPPER RESPIRATORY TRACT INFECTION
007-013-005	LOOSE STOOLS OCCASIONAL
007-015-005	DYSPEPSIA
007-015-005	HEARTBURN
007-015-005	WORSENING STOMACH PAIN (DYSPEPSIA)
007-057-001	ABDOMINAL BLOATING
007-057-001	INCREASED FLATULANCE
007-057-008	CHEST INFECTION (FLU LIKE SYMPTOMS)
007-057-008	TRANSIENT RASH R) LOWER LEG
007-057-025	PAPULAR NON-ITCHY, RADING, BROWN RASH
007-057-045	SORE THROAT
007-057-045	RHINNORRHEA
007-077-012	OCCASSIONAL RIGHT UPPER QUADRANT PAIN
007-077-012	BREATHLESSNESS FOR 3 DAYS
007-077-012	LOOSE STOOL

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

March 15 2006



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Kerry Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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Kenny Shade  
3/16/2006 02:02:31 PM  
CSO

Kathrine Laessig  
3/16/2006 02:33:47 PM  
MEDICAL OFFICER

## DSI CONSULT: Request for Clinical Inspections

**Date:** March 10, 2006

**To:** Constance Lewin, M.D., Acting Branch Chief, GCP1  
Antoine El-Hage, GCPB Reviewer, HFD-46

**cc:** Joseph Salewski, Acting Director, DSI, HFD-45  
Debra Birnkrant, M.D., Director, HFD-530

**From:** Kenny Shade, Regulatory Project Manager, HFD-530  
Division of Antiviral Products

**Subject:** **Request for Clinical Site Inspections**  
NDA 22-011  
Idenix Pharmaceuticals Inc.  
SEBIVO™ (telbivudine)

### Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. Please select any FOUR sites for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Number of Subjects that Discontinued	Indication
Site #008 Professor Yun-Fan Lian Liver Research Unit, Chang Gung Memorial Hospital 5, Fu-Shing St. Kweishan Taoyuan, 333 Taiwan, R.O.C.	NV-02B-007	60 patients	6	Treatment of chronic hepatitis B

## Request for Clinical Inspections

Site # (Name and Address)	Protocol #	Number of Subjects	Number of Subjects that Discontinued	Indication
Site #050 Dr. Satawat Thongsawat Division of Gastroenterology, Department of Medicine Faculty of Medicine, Chiang Mai University Hospital Chaing Mai Thailand	NV-02B-007	51 patients	4	Treatment of chronic hepatitis B
Site #057 Associate Professor Edward Gane Hepatitis Research Clinic Gastroenterology Department Middlemore Hospital Otahuhu Auckland New Zeland	NV-02B-007	66 patients	4	Treatment of chronic hepatitis B
Site #041 Dr. William Sievert Department of Medicine Monash Medical Center 246 Clayton Road Clayton, VIC 3168 Australia	NV-02B-007	22 patients	1	Treatment of chronic hepatitis B
Site #035 Dr. Jenny Heathcoate University Health Network Toronto Western Hospital 399 Bathurst Street, Fell Pavilion 6 <sup>th</sup> Floor Room 170 Toronto, Ontario, M5T 2S8 Canada	NV-02B-007	24 patients	2	Treatment of chronic hepatitis B

**International Inspections:**

We have requested inspections because (please check all that apply):

X There are insufficient domestic data

     Only foreign data are submitted to support an application

- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: SPECIFY

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) August 1, 2006. We intend to issue an action letter on this application by (division action goal date) October 16, 2006. The PDUFA due date for this application is October 30, 2006.

Should you require any additional information, please contact Kenny Shade at 301-796-0807.

Concurrence: (if necessary)

Katherine Laessig, M.D., Medical Team Leader  
Charlene Brown, M.D., Medical Reviewer  
Debra Birnkrant, M.D., Division Director

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/s/

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Debra Birnkrant  
3/13/2006 01:03:30 PM  
NDA 22-011

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011/SN-002  
**Drug:** SEBIVO™ (telbivudine)  
**Date:** March 13, 2006  
**To:** David Hallinan, Ph.D.  
**Sponsor:** Idenix Pharmaceuticals, Inc.  
**From:** Kenny Shade, JD, BSN  
**Through:** Charlene Brown, M.D., Clinical Reviewer  
**Concur:** Katherine Laessig, MD, Clinical Team Leader  
**Subject:** Clinical Reviewer Comments

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The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for SEBIVO™ (telbivudine) submitted February 24, 2006.

**Clinical Comments****Questions to the Agency**

1. As the 120-day safety update document is associated with the Summary of Clinical Safety and the Study Tagging File eCTD Specifications do not include a specific file-tag element for the safety updates required under 21 CFR 314.50(d)(5)(vi)(b), Idenix proposes to submit the update to Module 2, Section 2.7.4 and use the eCTD operation attribute value 'append' to associate it to the SCS. As was the case for the Clinical Summary post-text tables, the safety update post-text table would therefore be located in Module 5, Section 5.3.5.3. They would be associated with the SCS tables submitted in Sequence 0000 using the eCTD operation attribute value 'append'. Both the safety update and the post-text tables would possess unique filenames to differentiate them from the original files to which they have been appended.

Does the Agency agree with this approach?

*Agency's Response: Yes. In addition to the description above, please submit a guide that includes the description, location and names of the appended documents with your safety update submission.*

2. In accordance with 21 CFR 314.50(d) (5) (vi) (b), Idenix proposes to include any additional case report forms (CRFs) for each patient who died during a clinical study or who did not complete the study because of an adverse event up to the cutoff of 1 November 2005. This would result in approximately 34 new CRFs which will be filed to the relevant study using eCTD operation attribute value 'new'. The population for the study in decompensated patients, NV-02B-011, does not currently fall within the claimed indication of NDA 22-011. In addition, the ongoing study is currently blinded. Idenix would like to request a waiver for submission of CRFs from this study with this 120-day safety update.  
Does the Agency agree with this approach?

*Agency's Response: Yes, you may exclude CRFs from NV-02B-011. Please include any new CRFs, however, for all subjects who experienced SAEs and /or Grade 3/4 ALT elevations, whether or not they discontinued from the study. Include CRFs for all deaths, as you described. Also please include CRFs for all subjects that have discontinued up to the cutoff of November 1, 2005. Please ensure that a key is provided for CRFs that will be submitted with the 120-day safety update that includes the USUBJID and a short description of reason that a CRF is being provided for the subject (e.g. death due to car accident, etc.) The current Cardkey analysis dataset and the patient narratives do not efficiently provide this information. If such a key exists within the NDA submission, kindly disregard this request for a CRF key and please identify its location.*

3. Idenix proposes to submit eCRT for studies NV-02B-007, NV-02B-010, and NV-02B-015 as well as datasets containing the analyses of pooled safety data from study NV-02B-07 & NV-02B-015. The datasets containing 120-day safety update information will be associated to the appropriate studies using eCTD operation attribute value 'new'. As such, the NDA will contain datasets pertinent to the review of the clinical study reports as well as datasets pertinent to the review of the safety update information required under 21 CFR 314.50(d) (5) (vi)(b). The new datasets will be named in a manner that will differentiate them from the datasets that are supportive of the clinical study reports. The data definition information will be appended to any existing define.pdf using the eCTD operation attribute value 'append'. In case of the NV-02b-015 listings data and the pooled analyses data, the eCTD operation attribute value 'new' will be used for the data definition table documents as this will be the first instance of them in the NDA.

Idenix concludes that the content and format of the proposed 120-day safety update will provide the agency with all of the required information in a format consistent with the NDA currently under review.

Does the agency agree with this approach?

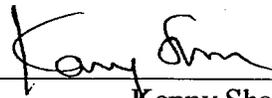
*Agency's Response: In addition to the pooled analyses of safety data for both NV-02B-00 and NV-02B-015 that you describe in your proposal, please also provide safety datasets (non-analyzed) with individual patient listings for NV-02B-015 as well as pooled (non-analyzed) dataset with individual patient listings from both NV-02B-007 and NV-02B-015. Similarly, provide a non-analyzed safety dataset with individual patient listings from NV-02B-010. This is akin to the approach used with the provision of both analysis and listings datasets in your original submission for NDA 22-011. Please continue to provide both the calendar date and study day variables (eg ONSETDSD, RESOLVDSD, DLDDTSD, ect.) with these datasets.*

March 13, 2006

*Also, please add a section to the 120-Day Safety Update Shell that includes summarizes the safety updates from each study separately. In other words, a short discussion of the safety findings and issues that arose in the intervening period from NV-02B-015, NV-02B-010, and NV-02B-007.*

*Also, please include AEs that occur up to 30 days after the last dose of study drug as on-treatment AEs in your safety analyses. The Division of Antiviral Products usually considers and AE to have occurred "on treatment" if it occurs while taking the study drug or up to 30 days after the last treatment dose.*

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.



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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011  
**Drug:** SEBIVO™ (telbivudine)  
**Date:** March 15, 2006  
**To:** David Hallinan, Ph.D.  
**Sponsor:** Idenix Pharmaceuticals, Inc.  
**From:** Kenny Shade, JD, BSN  
**Through:** Charlene Brown, M.D., Clinical Reviewer  
**Concur:** Katherine Laessig, MD, Clinical Team Leader  
**Subject:** Clinical Comments

The following comments related to the clinical datasets submitted for Protocol NV-02B-007 are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for Sebivo™ submitted December 30, 2005.

**Clinical Comments**

1. The variables DLDDT, Date of Last Dose (derived) and DLDDTSD, Study Day of DLDDT in your "Drug Dispensation" Individual Subject Listings Datasets is missing data for most of the study subjects. Is this because most of the subjects are still on study drug? Please clarify.
2. In the AE Individual Subject Listings Dataset, there are several rows which include patient information (ID, RX, age, gender, race, baseline date, stratification), but do not have any AE data (e.g. event, preferred term, soc, onset date, resolution date, etc), despite a Yes value for the AEYN variable. Please explain.
3. Also in the AE Individual Subject Listings Dataset, there is missing data for many subjects for the variables RESOLVDT and RESOLVSD, when ONSETDT and ONSETSD are provided. Does this mean that the AE had not resolved by the dataset lock date? Please clarify.
4. Please provide an abbreviated key or guide for the Case Report Forms (CRFs) that includes the reason the study, site, patient ID and the reason that a CRF is being provided for the patient.

March 15 2006

5. The analysis A\_AE datasets submitted use a Y/N variable to assess whether or not an AE occurred on treatment. Your definition of "on treatment" for this purpose is defined as an AE occurring during treatment or up to 7 days after the last dose of treatment. The Division of Antiviral Products usually considers an AE to have occurred "on treatment" if it occurs while taking the study drug or up to 30 days after the last treatment dose.
6. There are 25 adverse events for which the information regarding timing of either the onset of the adverse event (ONSETDSD or ONSETDT) or the resolution of the adverse event (RESOLVSD and RESOLVDT) or both are not provided. Although the Day of the Last Dose of Study Drug (DLDDTSD) is available is provided for the subjects with these AEs, it is still not possible to determine whether or not these AEs occurred on treatment without knowing the AE onset. Also, if the resolution date is not provided or occurs after the last dose of study drug, it is not possible to assess whether or not the AE occurred on treatment unless the AE onset is provided. Please provide this information for the following USUBJID/EVENT combinations from the AE dataset for Protocol NV-02B-007:

007-008-036	RIGHT UPPER QUADRANT PAIN
007-008-036	ARRHYTHMIA
007-008-036	FINGER JOINT PAIN
007-008-036	LEFT KNEE JOINT PAIN
007-008-036	LEFT SHOULDER PAIN
007-008-036	LOWER BACK PAIN
007-012-001	ABDOMINAL MUSCLE CRAMP
007-012-001	WEIGHT LOSS
007-012-015	CONSTIPATION
007-012-015	NUMBNESS AT FINGERTIP.
007-012-015	UPPER RESPIRATORY TRACT INFECTION
007-013-005	LOOSE STOOLS OCCASIONAL
007-015-005	DYSPEPSIA
007-015-005	HEARTBURN
007-015-005	WORSENING STOMACH PAIN (DYSPEPSIA)
007-057-001	ABDOMINAL BLOATING
007-057-001	INCREASED FLATULANCE
007-057-008	CHEST INFECTION (FLU LIKE SYMPTOMS)
007-057-008	TRANSIENT RASH R) LOWER LEG
007-057-025	PAPULAR NON-ITCHY, RADING, BROWN RASH
007-057-045	SORE THROAT
007-057-045	RHINNORRHEA
007-077-012	OCCASSIONAL RIGHT UPPER QUADRANT PAIN
007-077-012	BREATHLESSNESS FOR 3 DAYS
007-077-012	LOOSE STOOL

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March 15 2006

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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Kenny Shade  
3/16/2006 02:02:31 PM  
CSO

Kathrine Laessig  
3/16/2006 02:33:47 PM  
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-011

Idenix Pharmaceuticals Inc.  
Attention: David Hallinan, Ph.D.  
60 Hampshire Street  
Cambridge, MA 02139

Dear Dr. Hallinan:

Please refer to your December 30, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sebivo™ (telbivudine) 600 mg tablet.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 28, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

**Clinical Pharmacology**

1. Please provide the following information within 60 days from the date of this letter.

As discussed in the pre-NDA meeting, we would like you to conduct a PK/PD analysis to justify the proposed dose adjustment for patients with renal impairment.

Please submit the following information with your PK/PD analysis reports:

- All raw data that were used for population PK/PD analyses. Please include the following variables in the PD database: ID, treatment, time relative to the start of treatment, viral load, cell culture EC50 value, AUC, Ctrough, CD4<sup>+</sup> cell counts, and relevant adverse events. You may include other relevant variables in the PD database. The data should be submitted as SAS transport files.
- Data files (SAS transport files) used for modeling and simulation.
- Model and output files. All model files should be submitted as "txt" files. For example filename "test1.ctf" should be renamed as "test1\_ctl.txt".

**Microbiology**

2. Please include genotypic data of two patients, 004-003 and 116-060, in your NV-02B-RES1-seq-scrn.xpt file.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 796-0807 or (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Jeffrey Murray  
3/13/2006 02:10:59 PM



Food and Drug Administration  
Division of Antiviral Products  
Office of Antimicrobial Products  
Silver Spring, MD 20903

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011

**Drug:** SEBIVO™ (telbivudine)

**Date:** March 7, 2006

**To:** David Hallinan, Ph.D.

**Sponsor:** Idenix Pharmaceuticals, Inc.

**From:** Kenny Shade, JD, BSN

**Through:** Sung Rhee, Ph.D., Microbiology Reviewer  
Charlene Brown, M.D., Clinical Reviewer

**Concur:** Julian O'Rear, Ph.D., Microbiology Team Leader  
Katherine Laessig, MD, Clinical Team Leader

**Subject:** Microbiology Comments

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The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for Sebivo™ (telbivudine) submitted February 13, 2006.

**Microbiology Comments**

- 1. The description of resistance for LdT appears to be incomplete due to the limited number of samples analyzed. Please provide the reverse transcriptase genotype of the last on-therapy samples from the patients whose HBV viral load was = 10<sup>3</sup> copies/mL at 48 weeks (see list below).*

**FDA comment on Idenix's response:** The request for analyzing genotypes from individuals with viral loads of >10<sup>3</sup> copies/mL is consistent with the resistance data provided by other recent sponsors, with the analyses conducted by FDA, and with the information in the labels. Other sponsors have in fact provided more genotypic data than Idenix will have provided with these additional data.

Identification of resistant virus by viral load assessments includes not only those individuals whose viral load goes down and rises, but may also include patients whose viral load declines and plateaus to a "set point" above 10<sup>3</sup> copies/mL (when the time it takes for WT viral DNA

to decline below the set point is longer than the time for resistant virus to reach the set point). Additionally, FDA looks for baseline genotypic markers predictive of success or failure in the nonresponder and suboptimal responder populations, e.g. lamivudine resistance-associated mutations may lead to the development of entecavir resistance-associated mutations.

A more detailed analysis of the original resistance dataset has identified several subjects who withdrew at an early time and need not be analyzed, and a few subjects missed in the earlier analysis. An updated list without the original 19 for which data have been provided is attached (N=150). We appreciate Idenix's efforts to provide these data as promptly as possible.

2. *Please determine the in vitro combination activity relationships for telbivudine with approved HBV drugs and HIV NRTIs. For the HIV NRTIs, the effects of telbivudine on the anti-HIV activity need to be evaluated, as well as the effects of the NRTIs on the anti-HBV activity of the telbivudine.*

**FDA comment on Idenix's response:** The Agency is primarily concerned with the potential for antagonism as the sponsor recognizes. The adequacy of the submitted reports is a review issue.

3. *Please determine the antiviral activity in vitro of telbivudine for HBV genomes harboring the adefovir resistance-associated substitutions A181V and A181T.*

**FDA comment on Idenix's response:** The frequency of the adefovir resistance-associated amino acid substitution A181T is unclear at this time, as it may be underreported. The sponsor may forgo these studies for the time being with the understanding that additional studies may be required in the future if the frequency is found to be higher.

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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

Pat ID	Sample	Pat ID	Sample	Pat ID	Sample
003-065	WEEK 52	068-001	WEEK 52	116-018	WEEK 52
003-085	WEEK 52	068-017	WEEK 52	116-025	WEEK 52
003-124	WEEK 52	068-021	WEEK 52	116-045	WEEK 52
003-153	WEEK 52	070-011	WEEK 52	116-050	WEEK 52
003-164	WEEK 52	071-007	WEEK 52	116-059	WEEK 52
003-199	WEEK 52	071-013	WEEK 52	118-006	WEEK 52
003-211	WEEK 52	071-024	WEEK 52	118-008	WEEK 52
004-003	WEEK 52	071-027	WEEK 24/ET	119-005	WEEK 52
005-002	WEEK 52	071-041	WEEK 52	119-007	WEEK 52
005-007	WEEK 40/ET	071-043	WEEK 52	120-024	WEEK 52
005-014	WEEK 52	073-016	WEEK 52	120-027	WEEK 52
006-001	WEEK 52	079-008	WEEK 52	120-032	WEEK 52
007-041	WEEK 48/ET	080-008	WEEK 52	120-048	WEEK 52
008-046	WEEK 52	080-009	WEEK 52	122-003	WEEK 52
008-074	WEEK 52	083-003	WEEK 52	122-004	WEEK 52
008-092	WEEK 52	084-005	WEEK 52	122-015	WEEK 52
009-004	WEEK 52	084-008	WEEK 52	122-016	WEEK 52
010-002	WEEK 52	084-012	WEEK 52	122-028	WEEK 52
017-004	WEEK 52	087-009	WEEK 52	122-034	WEEK 52
019-003	WEEK 52	094-001	WEEK 52	122-044	WEEK 52
025-008	UNS-WK 40	095-006	WEEK 52	125-002	WEEK 52
025-011	WEEK 52	098-004	WEEK 52	126-004	WEEK 52
027-001	WEEK 24/ET	103-004	WEEK 52	126-007	WEEK 52
033-005	WEEK 52	104-001	WEEK 52	126-013	WEEK 52
033-011	WEEK 52	105-009	WEEK 52	126-027	WEEK 52
035-003	WEEK 52	105-012	UNS-WEEK 52	127-044	WEEK 52
035-007	WEEK 52	105-024	WEEK 52	130-016	WEEK 52
035-017	WEEK 52	105-029	WEEK 52	131-004	WEEK 52
035-026	WEEK 40	106-024	WEEK 52		
039-005	WEEK 52	106-032	WEEK 52		
039-007	WEEK 52	106-041	WEEK 52		
041-016	WEEK 52	108-003	WEEK 52		
041-027	WEEK 52	108-010	WEEK 52		
046-016	WEEK 52	108-013	WEEK 16		
050-023	WEEK 52	108-018	WEEK 52		
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050-060	WEEK 52	108-023	WEEK 52		
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053-010	WEEK 52	108-039	WEEK 52		
053-011	WEEK 52	108-044	WEEK 52		
053-016	WEEK 52	108-055	WEEK 52		
054-030	WEEK 52	108-059	WEEK 52		
055-008	WEEK 52	108-060	WEEK 52		
057-001	WEEK 52	108-062	WEEK 52		
057-030	WEEK 52	109-035	WEEK 52		
057-045	WEEK 52	109-037	WEEK 52		
057-050	WEEK 52	109-038	WEEK 52		
057-067	WEEK 52	109-042	WEEK 52		
057-088	WEEK 52	109-056	WEEK 52		
057-089	WEEK 52	109-059	WEEK 52		
057-095	WEEK 52	111-007	WEEK 52		
057-101	WEEK 52	112-006	WEEK 52		
057-123	WEEK 52	112-009	WEEK 52		
057-131	WEEK 52	112-017	WEEK 48		
058-015	WEEK 52	112-023	WEEK 52		
059-001	WEEK 52	113-010	WEEK 52		
061-039	WEEK 52	113-021	WEEK 52		
064-006	WEEK 52	114-012	WEEK 52		
065-018	WEEK 52	114-021	WEEK 52		
066-003	WEEK 52	114-030	WEEK 52		
066-017	WEEK 52	115-009	WEEK 52		

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/s/

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Kenny Shade  
3/9/2006 02:04:15 PM  
CSO

Kathrine Laessig  
3/9/2006 02:56:35 PM  
MEDICAL OFFICER



Food and Drug Administration  
Division of Antiviral Products  
Office of Antimicrobial Products  
Silver Spring, MD 20903

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011

**Drug:** SEBIVO™ (telbivudine)

**Date:** March 7, 2006

**To:** David Hallinan, Ph.D.

**Sponsor:** Idenix Pharmaceuticals, Inc.

**From:** Kenny Shade, JD, BSN

**Through:** Sung Rhee, Ph.D., Microbiology Reviewer  
Charlene Brown, M.D., Clinical Reviewer

**Concur:** Julian O'Rear, Ph.D., Microbiology Team Leader  
Katherine Laessig, MD, Clinical Team Leader

**Subject:** Microbiology Comments

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**Microbiology Comments**

- 1. The description of resistance for LdT appears to be incomplete due to the limited number of samples analyzed. Please provide the reverse transcriptase genotype of the last on-therapy samples from the patients whose HBV viral load was = 10<sup>3</sup> copies/mL at 48 weeks (see list below).*

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Additionally, FDA looks for baseline genotypic markers predictive of success or failure in the nonresponder and suboptimal responder populations, e.g. lamivudine resistance-associated mutations may lead to the development of entecavir resistance-associated mutations.

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- 2. Please determine the in vitro combination activity relationships for telbivudine with approved HBV drugs and HIV NRTIs. For the HIV NRTIs, the effects of telbivudine on the anti-HIV activity need to be evaluated, as well as the effects of the NRTIs on the anti-HBV activity of the telbivudine.*

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- 3. Please determine the antiviral activity in vitro of telbivudine for HBV genomes harboring the adefovir resistance-associated substitutions A181V and A181T.*

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---

Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

Enclosure: List of Patient IDs

Pat ID	Sample	Pat ID	Sample	Pat ID	Sample
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017-004	WEEK 52	087-009	WEEK 52	122-034	WEEK 52
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039-007	WEEK 52	106-041	WEEK 52		
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041-027	WEEK 52	108-010	WEEK 52		
046-016	WEEK 52	108-013	WEEK 16		
050-023	WEEK 52	108-018	WEEK 52		
050-048	WEEK 52	108-022	WEEK 52		
050-060	WEEK 52	108-023	WEEK 52		
051-023	WEEK 52	108-029	WEEK 52		
053-010	WEEK 52	108-039	WEEK 52		
053-011	WEEK 52	108-044	WEEK 52		
053-016	WEEK 52	108-055	WEEK 52		
054-030	WEEK 52	108-059	WEEK 52		
055-008	WEEK 52	108-060	WEEK 52		
057-001	WEEK 52	108-062	WEEK 52		
057-030	WEEK 52	109-035	WEEK 52		
057-045	WEEK 52	109-037	WEEK 52		
057-050	WEEK 52	109-038	WEEK 52		
057-067	WEEK 52	109-042	WEEK 52		
057-088	WEEK 52	109-056	WEEK 52		
057-089	WEEK 52	109-059	WEEK 52		
057-095	WEEK 52	111-007	WEEK 52		
057-101	WEEK 52	112-006	WEEK 52		
057-123	WEEK 52	112-009	WEEK 52		
057-131	WEEK 52	112-017	WEEK 48		
058-015	WEEK 52	112-023	WEEK 52		
059-001	WEEK 52	113-010	WEEK 52		
061-039	WEEK 52	113-021	WEEK 52		
064-006	WEEK 52	114-012	WEEK 52		
065-018	WEEK 52	114-021	WEEK 52		
066-003	WEEK 52	114-030	WEEK 52		
066-017	WEEK 52	115-009	WEEK 52		

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/s/

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Kenny Shade  
3/9/2006 02:04:15 PM  
CSO

Kathrine Laessig  
3/9/2006 02:56:35 PM  
MEDICAL OFFICER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**IND:** 22-011  
**Drug:** Telbivudine  
**Date:** February 6, 2006  
**To:** David Hallinan, Ph.D.  
**Sponsor:** Idenix Pharmaceuticals, Inc.  
**From:** Kenny Shade, JD, BSN  
**Through:** Charlene Brown, M.D., Clinical Reviewer  
**Concur:** Russell Fleischer, PA-C, M.P.H.  
**Subject:** Clinical Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for Telbivudine submitted December 30, 2005.

**Clinical Comments**

1. The format of the data in your NDA submission provides the calendar day, month and year instead of the study day for items such as the onset and resolution of symptoms. Please resubmit data listings that list both calendar dates and the study day. This will include datasets that have baseline dates, onset and/or resolution of symptom dates, dates of laboratory tests and /or biopsies, or any other calendar dates.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0807 if you have any questions regarding the contents of this transmission.

Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
2/6/2006 01:07:02 PM  
CSO

Russell Fleischer  
2/6/2006 01:13:04 PM  
MEDICAL OFFICER

**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-011

**Drug:** Telbivudine

**Date:** January 24, 2006

**To:** David Hallinan, Ph.D.

**Sponsor:** Idenix Pharmaceuticals, Inc.

**From:** Kenny Shade, JD, BSN

**Through:** Charlene Brown, M.D., Clinical Reviewer  
Sung Rhee, Ph.D., Microbiology Reviewer

**Concur:** Katherine Laessig, MD, Clinical Team Leader  
Julian O'Rear, Ph.D. Microbiology Team Leader

**Subject:** Microbiology Reviewer Comments

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The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-011 for telbivudine, submitted December 30, 2005.

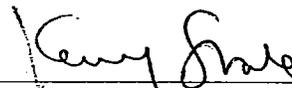
**Microbiology Comments**

1. The description of resistance for LdT appears to be incomplete due to the limited number of samples analyzed. Please provide the reverse transcriptase genotype of the last on-therapy samples from the patients whose HBV viral load was  $\geq 10^3$  copies/mL at 48 weeks (see list below).
2. Please determine the *in vitro* combination activity relationships for telbivudine with approved HBV drugs and HIV NRTIs. For the HIV NRTIs, the effects of telbivudine on the anti-HIV activity need to be evaluated, as well as the effects of the NRTIs on the anti-HBV activity of telbivudine.
3. Please determine the antiviral activity *in vitro* of telbivudine for HBV genomes harboring the adefovir resistance-associated substitutions A181V and A181T.

Subjects not reaching <1000 copies at week 52			
003-065	057-001	098-004	114-030
003-085	057-025	098-006	115-009
003-124	057-030	100-003	116-018
003-153	057-045	103-002	116-025
003-164	057-050	103-004	116-034
003-199	057-067	104-001	116-045
003-205	057-088	105-009	116-050
003-211	057-089	105-012	116-051
005-001	057-095	105-024	116-059
005-002	057-101	105-029	118-006
005-007	057-123	106-024	118-008
005-014	057-131	106-030	119-005
006-001	058-015	106-032	119-007
007-041	059-001	106-041	120-002
008-046	061-039	107-023	120-024
008-074	064-006	108-003	120-027
008-092	065-018	108-010	120-032
009-004	066-003	108-013	120-048
010-002	066-004	108-018	122-003
014-004	066-017	108-022	122-004
017-004	068-001	108-023	122-015
019-003	068-017	108-029	122-016
025-008	068-021	108-039	122-028
025-011	070-011	108-044	122-034
027-001	071-007	108-055	122-044
033-005	071-013	108-059	125-002
033-011	071-014	108-060	126-002
033-017	071-024	108-062	126-004
035-003	071-041	109-035	126-007
035-007	071-043	109-037	126-011
035-015	073-016	109-038	126-013
035-017	074-004	109-042	126-027
035-026	079-008	109-056	127-044
039-005	080-008	109-059	130-016
039-007	080-009	111-007	131-002
041-016	081-011	112-006	131-004
041-027	083-003	112-009	
044-004	084-005	112-017	
046-011	084-008	112-023	
053-011	084-012	113-010	
053-016	087-009	113-021	
054-030	094-001	114-012	
055-008	095-006	114-021	

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January 24, 2006



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Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
1/24/2006 09:48:47 AM  
CSO

Kathrine Laessig  
1/24/2006 10:55:32 AM  
MEDICAL OFFICER



NDA 22-011

**NDA ACKNOWLEDGMENT**

Idenix Pharmaceuticals, Inc.  
Attention: David Hallinan, Ph.D.  
60 Hampshire St.  
Cambridge, MA 02139

Dear Dr. Hallinan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Sebivo™ (telbivudine)

Review Priority Classification: Standard

Date of Application: December 30, 2005

Date of Receipt: December 30, 2005

Our Reference Number: NDA 22-011

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 28, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 30, 2006.

Under 21 CFR 314.102(c), you may request a meeting with the Division (to be held approximately 90 days from the above receipt data) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral and partial waiver for this application sent in your NDA dated December 30, 2005 received December 30, 2005. Decisions about pediatric deferrals and /or partial waiver will be considered as per the Pediatric Research Equity Act.

NDA 22-011

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Antiviral Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, call Kenny Shade, Regulatory Project Manager, at (301) 796-0807 or (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, M.D.  
Division Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

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Kenny Shade  
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CSO

Kathrine Laessig  
1/6/2006 02:00:01 PM  
MEDICAL OFFICER



IND 60,459

Idenix Pharmaceuticals Inc.  
Attention: David Hallinan, Ph.D.  
Vice President, Regulatory Affairs  
125 Cambridge Park Drive, 3rd floor  
Cambridge, MA 02140

Dear Dr. Hallinan:

Please refer to the meeting between representatives of your firm and FDA on June 17, 2002. The purpose of this End of Phase II meeting was to discuss the available safety and efficacy data from your completed/ongoing Phase I-II clinical studies with LdT, and your plan to initiate Phase III clinical trials in adult patients with chronic hepatitis B virus infection.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Nitin Patel, Regulatory Project Manager, at 301-827-2335.

Sincerely,

*{See appended electronic signature page}*

Anthony W. DeCicco, R.Ph.  
Chief, Project Management Staff  
Division of Antiviral Drug Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research

Attachment



**RECORD OF FDA/INDUSTRY MEETING**

**Date of Meeting:** June 17, 2002

**IND:** 60,459

**Drug:** Telbivudine (LdT)

**Sponsor:** Idenix Pharmaceuticals  
(formerly Novirio Pharmaceuticals)

**Indication:** Treatment of chronic hepatitis B infection

**Type of Meeting:** End of Phase II Meeting

**FDA Participants:**

Mark J. Goldberger, M.D., M.P.H., Office Director, ODEIV  
Debra B. Birnkrant, M.D., Division Director  
Jeffrey S. Murray, M.D., M.P.H., Deputy Division Director  
Katherine A. Laessig, M.D., Medical Team Leader  
Anthony W. DeCicco, R.Ph., Chief, Project Management Staff  
Ita S. Yuen, Ph.D., Pharmacologist  
Julian J. O'Rear, Ph.D., Microbiology Team Leader  
Robert O. Kumi, Ph.D., Acting Pharmacokinetics Team Leader  
Jenny H. Zheng, Ph.D., Pharmacokinetics Reviewer  
Greg Soon, Ph.D., Biometrics Team Leader  
Fraser B. Smith, Ph.D., Mathematical Statistician  
Stanka Kukich, M.D., Medical Team Leader  
Harry Haverkos, M.D., Medical Reviewer  
Sean Belouin, R.Ph., Regulatory Project Manager  
Jeff D. O'Neill, ACRN, BA, Regulatory Project Manager  
Nitin Patel, R.Ph., Regulatory Project Manager

**External Participants:**

Nathaniel Brown, M.D., Sr. VP, Hepatitis Clinical Research  
Maureen Myers, Ph.D., Sr. VP Clinical Research  
George Chao, Ph.D., VP, Biostatistics & Data Management  
David Standring, Ph.D., VP, Virology  
David Hallinan, Ph.D., VP, Regulatory Affairs  
Rumana Rahman, Manager, Regulatory Affairs

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**BACKGROUND:**

This End of Phase II (EOP2) meeting was held at the request of the Sponsor, Idenix Pharmaceuticals, to discuss the available safety and efficacy data from the Sponsor's completed/ongoing Phase I-II clinical studies with LdT, and the Sponsor's plan to initiate Phase III clinical trials in adult patients with chronic hepatitis B.

The Sponsor submitted an EOP2 meeting request and an Information Packet to the Division on May 2, 2002 (SN024). Prior to the meeting, a safety update (data cut-off June 10, 2002) and efficacy update (data cut-off May 28, 2002) were submitted to the Division on June 12, 2002 (SN029). A list of key questions for discussion at the meeting was also sent by telephone facsimile to Mr. Patel, the Regulatory Project Manager, on June 14, 2002.

**DISCUSSION:**

In addition to addressing the questions that were submitted by the Sponsor, the discussion covered the following topics: Phase III dose justification, protocol design, statistical considerations and resistance data. A brief summary of the agreements reached while discussing these topics is provided after the Division's comments to the Sponsor's questions.

**Questions that were provided for this discussion by the Sponsor on June 14, 2002:**

Please note, the Sponsor's questions are shown in regular font, followed by the Division's response in bold font.

1. Is combining HBeAg+ and HBeAg- patients still acceptable?

**The Division was in agreement that this was acceptable.**

2. Can chronic hepatitis B be alternately defined as HBsAg+ at screen with compatible histology (chronic viral hepatitis) and elevated ALT (>1.3xULN) ?

**The Division agreed with this definition.**

3. Does FDA agree with composite endpoint of "therapeutic response" (HBeAg loss or ALT normalization; and HBV DNA < 10<sup>5</sup> copies/ml)?

**The Division needs to obtain feedback regarding histology being the primary endpoint at the HBV-directed Advisory Committee meeting on August 7, 2002. Therefore, no decision has been made yet regarding the acceptability of the Sponsor's primary efficacy endpoint.**

4. Does FDA have a preferred histologic scoring system? (Knodell, Ishak, Metavir)

**The Division did not indicate a strong preference.**

5. Is the robust, single study acceptable as the primary basis for FDA approval? – together with Phase I-IIb data and pilot data in 50-100 decompensated patients.

**The Division agreed that with additional supportive data, the single study as presented plus a small study in decompensated patients is acceptable as the primary basis of approval. The Division outlined some of the risks involved in a single Phase 3 study, such as a statistical risk from marginal efficacy results, and the sample size may not be large enough to show differences due to race or geography.**

6. How important is a placebo control in the Phase III study?

**The Division indicated that the placebo design option may be scientifically the most sound, but the Division does understand the difficulties pursuing this design. The Division feels that if the Sponsor cannot conduct the placebo-controlled study, then option 1 (active control design) will be acceptable.**

7. Does FDA agree with the 15% non-inferiority criterion for Option 1?

**The Division stated that the 15% delta for the non-inferiority active-controlled study is acceptable if histology is the primary efficacy endpoint. It may also be acceptable for the proposed therapeutic response primary endpoint, however, the Division will provide feedback to the Sponsor within 1 week regarding this point.**

8. Will FDA allow a superiority claim if  $p=0.00125$  for Option 1?

**The Division stated that for the single combined Phase III trial, showing that the lower limit of the one-sided  $(100 - 0.125/2=)$  99.9375% confidence interval on the difference in response rates is  $>0\%$ , may not be sufficient to make a superiority claim in the label for LdT over the comparator lamivudine. This will be a review issue and clinical significance and safety issues will be considered for this decision.**

9. Can  $\alpha = 0.00125$  be limited to 1<sup>o</sup> comparison, with 0.05 for others?

**The Division will provide feedback to the Sponsor within 1 week regarding this point.**

**Summary of the other agreements that were reached during the discussion:**

- The 600 mg LdT dose was considered acceptable as the appropriate dose in the Phase 3 study.
- Biopsies will need to be done at Year 1 and be included as part of the NDA.
- HBsAg is only required at screening, however, and does not need to be confirmed 6 months prior.

**ACTIONS:**

1. The Division will provide feedback to the Sponsor concerning questions 7 and 9.
2. The Sponsor will provide a draft report summarizing the resistance data by mid August prior to start up of the Phase 3 trial.
3. The Sponsor will submit a protocol outline/synopsis for LdT in decompensated HBV patients.

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/s/

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Tony DeCicco  
8/21/02 11:29:21 AM