EXCLUSIVITY SUMMARY

NDA # 22018 SUPPL # HFD #

Trade Name  NA

Generic Name  Lamivudine and Zidovudine Tablets, 150 mg/300 mg

Applicant Name  Pharmacare Limited t/a Aspen Pharmacare, South Africa

Approval Date, If Known  17 March 2017

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

      505(b)(2)

   b) 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:
c) Did the applicant request exclusivity?  

YES ☐  NO ☒  

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


d) 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
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# 20857 COMBIVIR (lamivudine and zidovudine) tablets, 150 mg/300 mg

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 ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

   a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

   Investigation #1  !
   IND #  YES ☐  ! NO ☐  ! Explain:

   Investigation #2  !
   IND #  YES ☐  ! NO ☐  ! Explain:
(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant’s predecessor in interest provided substantial support for the study?

Investigation #1
YES □ ☐ NO □ ☐
Explain:

Investigation #2
YES □ ☐ 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: Monica Zeballos
Title: Program Coordinator
Date: 24March2017
Name of Division Director signing form: Debra Birnkrant
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA I ZEBALLOS
03/24/2017

DEBRA B BIRNKRANT
03/24/2017
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>22018</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLA #</td>
<td></td>
<td>BLA Supplement #</td>
<td>(an action package is not required for SE8 or SE9 supplements)</td>
</tr>
</tbody>
</table>

| Proprietary Name: | None |
| Established/Proper Name: | Lamivudine and Zidovudine |
| Dosage Form: | Tablets, 150 mg/300 mg |

| Applicant: | Pharmacare Limited t/a Aspen Pharmacare, South Africa |
| Agent for Applicant (if applicable): | Diana Slone, Lachman Consultants Services, Inc. |

| RPM: | Monica Zeballos |
| Division: | DAVP |

| NDA Application Type: | ☐ 505(b)(1) | ☒ 505(b)(2) |
| Efficacy Supplement: | ☐ 505(b)(1) | ☐ 505(b)(2) |

| BLA Application Type: | ☐ 351(k) | ☐ 351(a) |
| Efficacy Supplement: | ☐ 351(k) | ☐ 351(a) |

For **ALL 505(b)(2) applications**, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
  - ☒ No changes
  - ☐ New patent/exclusivity (notify CDER OND IO)
  - Date of check: __________

*Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.*

### Actions

- **Proposed action**
- User Fee Goal Date is **Sunday, 19 March 2017 but taken action 17 March 2017**
- **Previous actions (specify type and date for each action taken)**

  - ☐ None
  - TA on 23 Aug 2006 for PEPFAR use

### If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

*Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain*

- ☐ Received

### Application Characteristics

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1. The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

2. **For resubmissions**, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

3. Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 4071345

Version: 01/04/17
Review priority: [ ] Standard  [ ] Priority  
Chemical classification (new NDAs only):  
(Confirm chemical classification at time of approval)  
[ ] Fast Track  [ ] Rx-to-OTC full switch  
[ ] Rolling Review  [ ] Rx-to-OTC partial switch  
[ ] Orphan drug designation  [ ] Direct-to-OTC  
[ ] Breakthrough Therapy designation  

(Note: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CSM SharePoint)  

NDAs: Subpart H  
[ ] Accelerated approval (21 CFR 314.510)  [ ] Accelerated approval (21 CFR 601.41)  
[ ] Restricted distribution (21 CFR 314.520)  [ ] Restricted distribution (21 CFR 601.42)  
[ ] Approval based on animal studies  [ ] Approval based on animal studies  

[ ] Submitted in response to a PMR  [ ] REMS: [ ] MedGuide  
[ ] Submitted in response to a PMC  [ ] Communication Plan  
[ ] Submitted in response to a Pediatric Written Request  [ ] ETASU  
[ ] Comments:  This is a class 2 resubmission to a TA requesting final approval after all the innovator listed patents for COMBIIVIR have expired.  

BLAs: Subpart E  
[ ] Accelerated approval (21 CFR 314.510)  [ ] Accelerated approval (21 CFR 601.41)  
[ ] Restricted distribution (21 CFR 314.520)  [ ] Restricted distribution (21 CFR 601.42)  
[ ] Approval based on animal studies  [ ] Approval based on animal studies  

[ ] Submitted in response to a PMR  [ ] REMS: [ ] MedGuide  
[ ] Submitted in response to a PMC  [ ] Communication Plan  
[ ] Submitted in response to a Pediatric Written Request  [ ] ETASU  
[ ] REMS: [ ] MedGuide w/o REMS  
[ ] REMS not required  

Public communications (approvals only)  
- Office of Executive Programs (OEP) liaison has been notified of action  
  - [ ] Yes  [ ] No  
- Indicate what types (if any) of information were issued  
  - None  
  - FDA Press Release  
  - FDA Talk Paper  
  - CDER Q&As  
  - Other  

Exclusivity  
- Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?  
  - [ ] No  [ ] Yes  
- If so, specify the type  

Patent Information (NDAs only)  
- Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.  
  - [ ] Verified  
  - Not applicable because drug is an old antibiotic. This is a 505b2 relied upon COMBIIVIR  

(CONTENTS OF ACTION PACKAGE)  

Officer/Employee List  
- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)  
  - [ ] Included  
- Documentation of consent/non-consent by officers/employees  
  - [ ] Included  

Reference ID: 4071345
### Action Letters

- **Copies of all action letters (including approval letter with final labeling)**
  - Action(s) and date(s)
    - 1) Approval 14March2017
    - 2) TA 23Aug2006

### Labeling

- **Package Insert (write submission/communication date at upper right of first page of PI)**
  - Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)
    - Included
  - Original applicant-proposed labeling
    - Included

- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)**
  - Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)
    - Included
  - Original applicant-proposed labeling
    - Included

- **Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)**
  - Most-recent draft labeling
    - Included

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) (indicate date(s))
  - Review(s) (indicate date(s))

- **Labeling reviews (indicate dates of reviews)**

### Administrative / Regulatory Documents

- **RPM Filing Review^4^ Memo of Filing Meeting (indicate date of each review)**
  - RPM: None 13March2017
  - DMEPA: None 13March2017
  - DMPP/PLT (Drisk): None
  - OPDP: None 13March2017
  - SEALD: None
  - CSS: None
  - Product Quality: None 06March2017
  - Other: None

- **All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee**
  - Not a (b)(2) 16March2017

- **NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)**
  - Completed (Do not include)

- **Application Integrity Policy (AIP) Status and Related Documents**
  - http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm
    - Applicant is on the AIP
      - Yes ☑ No

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^4^ Filing reviews for scientific disciplines are NOT required to be included in the action package.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>This application is on the AIP</td>
<td>□ Yes  □ No</td>
</tr>
<tr>
<td>- If yes, Center Director’s Exception for Review memo <em>(indicate date)</em></td>
<td></td>
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<tr>
<td>- If yes, OC clearance for approval <em>(indicate date of clearance communication)</em></td>
<td></td>
</tr>
<tr>
<td>Pediatrics <em>(approvals only)</em></td>
<td></td>
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<tr>
<td>- Date reviewed by PeRC</td>
<td></td>
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<tr>
<td>If PeRC review not necessary, explain: This 505(b)(2) NDA did not trigger PREA because it is not for a new indication, new dosing regimen, new active ingredient, new dosage form or new route of administration.</td>
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<tr>
<td>Breakthrough Therapy Designation</td>
<td>□ N/A</td>
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<tr>
<td>Breakthrough Therapy Designation Letter(s) <em>(granted, denied, an/or rescinded)</em></td>
<td></td>
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<tr>
<td>CDER Medical Policy Council Breakthrough Therapy Designation</td>
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<tr>
<td>Determination Review Template(s) <em>(include only the completed template(s) and not the meeting minutes)</em></td>
<td></td>
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<tr>
<td>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Recission Template(s) <em>(include only the completed template(s) and not the meeting minutes)</em></td>
<td></td>
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<tr>
<td><em>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</em></td>
<td></td>
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<tr>
<td>Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division <em>(e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.)</em> <em>(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</em></td>
<td>Included</td>
</tr>
<tr>
<td>Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division <em>(e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</em></td>
<td>None</td>
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<tr>
<td>Minutes of Meetings</td>
<td></td>
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<tr>
<td>- If not the first review cycle, any end-of-review meeting <em>(indicate date of mtg)</em></td>
<td>□ N/A or no mtg</td>
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<tr>
<td>- Pre-NDA/BLA meeting <em>(indicate date of mtg)</em></td>
<td>□ No mtg</td>
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<td>- EOP2 meeting <em>(indicate date of mtg)</em></td>
<td>□ No mtg</td>
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<tr>
<td>- Mid-cycle Communication <em>(indicate date of mtg)</em></td>
<td>□ N/A</td>
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<tr>
<td>- Late-cycle Meeting <em>(indicate date of mtg)</em></td>
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<td>- Other milestone meetings *(e.g., EOP2a, CMC focused milestone meetings) <em>(indicate dates of mtgs)</em></td>
<td>None</td>
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<tr>
<td>Advisory Committee Meeting(s)</td>
<td>□ No AC meeting</td>
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<td>- Date(s) of Meeting(s)</td>
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## Decisional and Summary Memos

<table>
<thead>
<tr>
<th>Topic</th>
<th>Status</th>
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<tbody>
<tr>
<td>Office Director Decisional Memo <em>(indicate date for each review)</em></td>
<td>□ None</td>
</tr>
<tr>
<td>Division Director Summary Review <em>(indicate date for each review)</em></td>
<td>□ None</td>
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<tr>
<td>1) Approval 15March2017</td>
<td></td>
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<tr>
<td>2) TA 23Aug2006</td>
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<tr>
<td>Cross-Discipline Team Leader Review <em>(indicate date for each review)</em></td>
<td>□ None</td>
</tr>
<tr>
<td>PMR/PMC Development Templates <em>(indicate total number)</em></td>
<td>□ None</td>
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</table>
### Clinical

- **Clinical Reviews**
  - Clinical Team Leader Review(s) *(indicate date for each review)*
  - Clinical review(s) *(indicate date for each review)*
  - Social scientist review(s) if OTC drug *(indicate date for each review)*
  - Financial Disclosure reviews(s) or location/date if addressed in another review OR
    - If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*
    - Clinical reviews from immunology and other clinical areas/divisions/centers *(indicate date of each review)*
  - Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*

- **Risk Management**
  - REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))*
  - REMS Memo(s) and letter(s) *(indicate date(s))*
  - Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*

- **OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*

### Clinical Microbiology

- Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*
- Clinical Microbiology Review(s) *(indicate date for each review)*

### Biostatistics

- Statistical Division Director Review(s) *(indicate date for each review)*
- Statistical Team Leader Review(s) *(indicate date for each review)*
- Statistical Review(s) *(indicate date for each review)*

### Clinical Pharmacology

- Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*
- Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*
- Clinical Pharmacology review(s) *(indicate date for each review)*
- OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*

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5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
## Nonclinical

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<thead>
<tr>
<th>Discipline/Review</th>
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</thead>
<tbody>
<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
</tr>
<tr>
<td>- ADP/T Review(s) <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>- Supervisory Review(s) <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>- Pharm/tox review(s), including referenced IND reviews <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>- Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>- Statistical review(s) of carcinogenicity studies <em>(indicate date for each review)</em></td>
</tr>
<tr>
<td>- ECAC/CAC report/memo of meeting</td>
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<tr>
<td>- OSI Nonclinical Inspection Review Summary <em>(include copies of OSI letters)</em></td>
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## Product Quality

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<tr>
<td>- Product Quality Discipline Reviews 6</td>
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<tr>
<td>- Tertiary review <em>(indicate date for each review)</em></td>
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<tr>
<td>- Secondary review *(e.g., Branch Chief) <em>(indicate date for each review)</em></td>
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<tr>
<td>- Integrated Quality Assessment <em>(contains the Executive Summary and the primary reviews from each product quality review discipline)</em> <em>(indicate date for each review)</em></td>
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<tr>
<td>- Reviews by other disciplines/divisions/Centers requested by product quality review team <em>(indicate date of each review)</em></td>
</tr>
<tr>
<td>- Environmental Assessment *(check one) <em>(original and supplemental applications)</em></td>
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<tr>
<td>- Categorical Exclusion *(indicate review date) <em>(all original applications and all efficacy supplements that could increase the patient population)</em></td>
</tr>
<tr>
<td>- Review &amp; FONSI <em>(indicate date of review)</em></td>
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<tr>
<td>- Review &amp; Environmental Impact Statement <em>(indicate date of each review)</em></td>
</tr>
<tr>
<td>- Facilities Review/Inspection</td>
</tr>
<tr>
<td>- Facilities inspections *(indicate date of recommendation) within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) <em>(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</em></td>
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6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Reference ID: 4071345
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>For all 505(b)(2) applications:</strong></td>
</tr>
<tr>
<td>- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
</tr>
<tr>
<td>[X] No changes</td>
</tr>
<tr>
<td>[ ] New patent/exclusivity <em>(Notify CDER OND IO)</em></td>
</tr>
<tr>
<td>- Finalize 505(b)(2) assessment</td>
</tr>
<tr>
<td>[X] Done</td>
</tr>
<tr>
<td><strong>For Breakthrough Therapy (BT) Designated drugs:</strong></td>
</tr>
<tr>
<td>- Notify the CDER BT Program Manager</td>
</tr>
<tr>
<td>[ ] Done</td>
</tr>
<tr>
<td><em>(Send email to CDER OND IO)</em></td>
</tr>
<tr>
<td><strong>For products that need to be added to the flush list (generally opioids): Flush List</strong></td>
</tr>
<tr>
<td>[ ] Done</td>
</tr>
<tr>
<td>- Notify the Division of Online Communications, Office of Communications</td>
</tr>
<tr>
<td><strong>Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</strong></td>
</tr>
<tr>
<td>[ ] Done</td>
</tr>
<tr>
<td><strong>If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</strong></td>
</tr>
<tr>
<td>[ ] Done</td>
</tr>
<tr>
<td><strong>Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</strong></td>
</tr>
<tr>
<td>[ ] Done</td>
</tr>
<tr>
<td><strong>Ensure Pediatric Record is accurate</strong></td>
</tr>
<tr>
<td>[ ] Done</td>
</tr>
<tr>
<td><strong>Send approval email within one business day to CDER-APPROVALS</strong></td>
</tr>
<tr>
<td>[X] Done</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA I ZEBALLOS
03/17/2017

Reference ID: 4071345
From: Zeballos, Monica
Sent: Thursday, March 16, 2017 8:46 AM
To: Zeballos, Monica
Cc: Schumann, Katherine; Goldstein, Beth A (Duvall); Sharma, Khushboo; Holovac, Mary Ann
Subject: PEPFAR NDA 22018 lamivudine/zidovudine - cleared for full approval
Attachments: NDA22018_505(b)(2) Assessment_March2017.doc

Monica,

The subject application was discussed via email with the committee. The application is cleared for action from a 505(b)(2) perspective.

No further changes are needed on the 505(b)(2) assessment before archiving into darts prior to taking approval action.

Please let me know if you have any questions.

Mary Ann

From: Zeballos, Monica
Sent: Wednesday, March 15, 2017 3:45 PM
To: Holovac, Mary Ann
Cc: Schumann, Katherine
Subject: RE: 505(b)(2) assessment for PEPFAR NDA 22018 seeking final approval

Thanks Mary Ann.

I revised the assessment for completeness and it’s attached.

Monica

From: Holovac, Mary Ann
Sent: Wednesday, March 15, 2017 9:46 AM
To: Zeballos, Monica; Schumann, Katherine
Subject: RE: 505(b)(2) assessment for PEPFAR NDA 22018 seeking final approval

I’ll send you a clearance email once the legal folks give their blessing.

From: Zeballos, Monica
Sent: Wednesday, March 15, 2017 9:43 AM
To: Holovac, Mary Ann; Schumann, Katherine
Subject: RE: 505(b)(2) assessment for PEPFAR NDA 22018 seeking final approval

That’s great. Many thanks to both.

Do I need to do anything additional from my end?

From: Holovac, Mary Ann
Sent: Wednesday, March 15, 2017 9:29 AM
Hello Diana,

Please find below our final revisions for the PI and container/carton labels for NDA 22018. The attached PI contains all the revisions conveyed to you via email on 10March2017 and it incorporates the phone number for reporting suspected adverse reactions you provided to me via email on 13March2017. You can officially submit the clean version for the PI and revised container/carton labels as final printed labeling after the goal date.

Labeling Revisions for the Package Insert

1. Please find attached our final labeling revisions on tracked changes for the PI. Please review them and let me know if Pharmacare accepts them. If yes, please send me via email a clean version in word by this Thursday, 16March2017 or sooner, as this will served as the agreed-upon labeling text for the PI.

Labeling Revisions for the Container and Carton Labels

2. In addition to the labeling revisions conveyed to you on 10March2017, please add the lot number and expiration date to the immediate container label per 21 CFR 201.10(j)(1) and 21 CFR 201.17, respectively. Ensure that the lot number is clearly differentiated from the expiration date to reduce the risk of medication errors resulting from administration of expired medication. Please send me via email revised mock ups by this Thursday, 16March2017 or sooner, as these will served as the agreed-upon labeling for the container/carton labels.

Please let me know if you have any questions.

Best regards,

Monica
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/s/

MONICA I ZEBALLOS
03/14/2017
Hello Diana,

Please find below comments for NDA 22018 as heads up. Please provide a response to comment 1 for the PI right away and be ready to provide a response to comments 2 and 3 for the labels next week. I’ll send our final labeling revisions (both for the PI and container and carton labels) by Tuesday, March 14, 2017. I’ll incorporate comments 2, 4 and 5 for the PI.

**Labeling Revisions for the Package Insert**

1. Highlights section: For reporting suspected Adverse Reaction (AR), the manufacturer must use a U.S. phone number (toll-free number is strongly recommended, but not required) and not a foreign phone number. The U.S. phone number does not have to be a dedicated phone number for AR reporting.

**Labeling Revisions for the Package Insert and Container and Carton Labels**

2. In consideration of the USP Monograph, and the demonstrated stability of your tablets under long-term stability studies at 30°C/75%RH, we recommend that the storage statements in Section 16 and on the bottle label be modified to read: “Store between 2°C and 30°C (36°F - 86°F). Protect from moisture and light.”

3. Please revise the name of the product on the bottle label and throughout the prescribing information to read: “Lamivudine and Zidovudine Tablets”

4. Please modify the list of inactive ingredients in Section 11 to be in alphabetical order: “Each tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, sodium starch glycollate, and talc.”

5. Please modify the statement in Section 16 to read: “60 Tablets/Bottle with desiccant, induction seal and child-resistant cap (NDC 52719-760-59).”

**User Fee**

6. Pharmacare will not be subject to an application fee for Lamivudine and Zidovudine Tablets, 150 mg/300 mg, but should be aware that it may be subject to the program fees if it receives final approval for NDA 22018. Pharmacare can consider requesting a waiver of those program fees if it believes it fits the criteria set forth in the guidance for industry User Fee Waivers, Reductions, and Refund for Drug

If you have any questions, please let me know.

Monica

CONFIDENTIALITY NOTE: This e-mail and any files transmitted are intended only for the use of the individual or entity to whom they are addressed, and may contain information that is privileged, confidential and exempt from disclosure under applicable law. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or use of any of the information is PROHIBITED.
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/s/

MONICA I ZEBALLOS  
03/10/2017  
This IR was emailed to applicant on 24Feb2017, but processed in DARRTS on 10March2017
Dear Ms. Sloane:

Please refer to your New Drug Application (NDA) dated September 17, 2016, received September 19, 2016 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Lamivudine and Zidovudine Tablets, 150 mg/300 mg

We are reviewing the Chemistry, Manufacturing and Control sections of your submission and have the following comments and information requests. We request a written response by Wednesday November 16, 2016, in order to continue our evaluation of your NDA.

Please amend your NDA by submitting the following information:

1. The current Drug Product Specification (in 3.2.P.5)
2. Clarification of whether the
3. An overview of the changes made since NDA 22018 received tentative approval in 2006
4. Verification that the intended packaging configuration will use the same materials and suppliers as submitted in the amendment dated Aug 26, 2014 and subsequent amendments (HDPE bottle, Child-Resistant cap, induction seal, desiccant disc). Clarify whether any stability data are available with the desiccant disc supplied by .

If you have any questions, please contact me at (301) 796 4013, or luz.e.rivera@fda.hhs.gov
Sincerely,

(See appended electronic signature page)

LCDR Luz E Rivera, Psy.D.
Quality Assessment Lead (Acting), Div. I, Branch I
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
NDA 22018

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Lachman Consultant Services Inc.
Attention: Diana Sloane, Senior Associate
U.S. Agent for Pharmacare Limited in South Africa
1600 Stewart Avenue, Suite 604
Westbury, NY 11590

Dear Ms. Sloane:

We acknowledge receipt on September 19, 2016, of your September 17, 2016, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following drug product:

- Lamivudine and Zidovudine Tablets, 150 mg/300 mg

We consider this a complete, class 2 response to our August 23, 2006, action letter. Therefore, the user fee goal date is March 19, 2017.

If you have any questions, please call me at (301) 796-0840 or via email at monica.zeballos@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Monica Zeballos, Pharm.D.
Program Coordinator
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA I ZEBALLOS
10/20/2016
NDA 22-018: N-000
Pharmacare Ltd
Attn: Keith Guinta
U.S. Agent for Aspen Pharmacare
76 South Orange Ave., Suite 203
South Orange, NJ 07079

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the
(b)(4).

Since 2000, FDA has conducted several comprehensive inspections of bioequivalence studies in which the bioanalytical analysis was conducted by
The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following:

- Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
- Failure to investigate anomalous results.
- Lack of assay reproducibility between original and repeat results.
- Assay accuracy not assured under the conditions of sample processing.
- Biased exclusion of study data resulting in the acceptance of failed runs.
- Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.

As a result of these findings, agreed to conduct an audit of data from all its bioequivalence studies generated from the
However, FDA identified significant deficiencies with the audit during its most recent inspection. Thus, serious questions remain about the validity of any data generated by in studies during this time period that have not been inspected by FDA. In view of these findings, FDA is informing holders of approved NDAs of these issues.
The impact of the data from these studies (which may include bioequivalence, pharmacokinetic, drug-drug interaction and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us within 30 days of receipt of this letter if you have submitted any studies conducted during the time period of concern. Please submit information on each of the studies submitted, including supplement number (if appropriate), study name/protocol number, and date of submission. This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

Once we have made an assessment regarding the potential impact of these data, we will contact you regarding the steps that need to be taken, if any, to assure the accuracy of the data submitted to your application.

If you have any questions, call Vasavi Reddy, Regulatory Project Manager, at 301-796-0793.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, MD  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research
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/s/
---------------------
Beth Duvall-Miller
1/31/2007 10:35:31 AM
for Division Director
MEMORANDUM

DATE: July 24, 2006

TO: Keith Giunta, U.S. Agent for Aspen Pharmacare

FROM: Vasavi T. Reddy, R.Ph. MPH, Regulatory Project Manager, DAVP

THROUGH: Rao Kambhampati, Ph.D., Chemistry Reviewer, ONDQA, DPA2
Norman Schmuff, Ph.D., Chemistry Branch Chief, ONDQA, DPA2

NDA: 22-018

Drug: Lamivudine/Zidovudine Tablets

Subject: Carton & Label Recommendations

Please address the following Chemistry, Manufacturing, and Controls (CMC) recommendations that are related to the NDA# 22-018 for lamivudine 150 mg/zidovudine 300 mg tablets carton and Package Insert:

Carton Label:

1. On the side of the carton label, please change "" to "Zidovudine 300 mg"

2. On the the carton label, change Tablets" to "Lamivudine/Zidovudine Tablets"

3.

4. On the carton label, please delete ASPEN and its monogram and delete either

5. On the carton label, change "".

6. On the carton label, please add "".
Package Insert:
CMC changes to the Description & How Supplied Sections of the label

Drug Name (Title): Please change (0. [4]) to Lamivudine 150 mg/Zidovudine 300 mg Tablets

DESCRIPTION
Lamivudine/Zidovudine Tablets: tablets are combination tablets containing lamivudine and zidovudine. Lamivudine and zidovudine which are synthetic nucleoside analogues with (b) activity against human immunodeficiency virus (HIV). Lamivudine/Zidovudine Tablets are for oral administration. Each tablet contains 150 mg of lamivudine and 300 mg of zidovudine, and the inactive ingredient colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycollate, talc,

Lamivudine: The chemical name of lamivudine is (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiocytidine. It has a molecular formula of C₈H₁₁N₃O₂S and a molecular weight of 229.3. It has the following structural formula:

![Lamivudine Structural Formula](image)

Lamivudine is a white to off-white crystalline solid

Zidovudine: The chemical name of zidovudine is 3'-azido-3'-deoxythymidine. It has a molecular formula of C₁₀H₁₃N₅O₄ and a molecular weight of 267.24. It has the following structural formula:
Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.

**HOW SUPPLIED**

150 mg of lamivudine are white to off-white, slightly mottled, oval, bevelled with one side. They are

Store

If you have any questions, please contact me at 301-796-0793 or via email at Vasavi.reddy@fda.hhs.gov

Thank you,

Vasavi Reddy

Vasavi T. Reddy, R.Ph., MPH, LCDR., USPHS
Sr Program Management Officer Consultant, DAVDP
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/s/
---------------------
Vasavi Reddy
7/24/2006 01:06:04 PM
CSO

Norman Schmuff
7/26/2006 05:36:17 PM
CHEMIST
DATE: July 7, 2006

TO: Keith Giunta, U.S. Agent for Aspen Pharmacare

FROM: Vasavi T. Reddy, R.Ph. MPH, Regulatory Project Manager, DAVP

THROUGH: Rao Kambhampati, Ph.D., Chemistry Reviewer, ONDQA, DPA2
         Norman Schmuff, Ph.D., Chemistry Branch Chief, ONDQA, DPA2

NDA: 22-018

Drug: Lamivudine/Zidovudine Tablets

Subject: Information Request

Please address the following Chemistry, Manufacturing, and Controls (CMC) comments and recommendations that are related to the NDA# 22-018 for lamivudine 150 mg/zidovudine 300 mg tablets:

1. Please provide summarized comparative batch analysis and stability study results for the lamivudine/zidovudine tablet batches and also include the following information:

   a) Batch number, batch size, date of manufacturing, name and site of manufacturing for the lamivudine and zidovudine drug substances.

   b) Batch number, batch size, date of manufacturing, name and site of manufacturing, process used for manufacturing, and packaging configuration used for stability studies and stability study results for the lamivudine/zidovudine tablets. If available, also include results for additional batches that were manufactured at the [REDACTED] for the lamivudine component.

2. Please provide updated stability study results for the lamivudine/zidovudine tablets including those that were manufactured at [REDACTED]. Please also include interpretation of the stability study results.
3. Please provide batch analysis results for the lamivudine/zidovudine tablets that were manufactured using lamivudine and zidovudine drug substances and zidovudine drug substance and, compare these results with the tablets that were manufactured at the (US DMF quality) lamivudine and zidovudine drug substances. Also provide stability study results, if available.

In addition we have the following general comment:

4. In future please submit the NDA information as according to the ICH CTD format or U.S. FDA format.

If you have any questions, please contact me at 301-796-0793 or via email at Vasavi.reddy@fda.hhs.gov

Thank you,

Vasavi Reddy

Vasavi T. Reddy, R.Ph., MPH, LCDR., USPHS
Sr Program Management Officer Consultant, DAVDP
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/s/
---------------------
Vasavi Reddy
7/7/2006 02:01:22 PM
CSO

Norman Schmuff
7/11/2006 08:10:11 AM
CHEMIST
DATE: July 5, 2006

TO: Keith Giunta, U.S. Agent for Aspen Pharmacare

FROM: Vasavi T. Reddy, R.Ph. MPH, Regulatory Project Manager, DAVP

THROUGH: Vikram Arya, Ph.D. Clinical Pharmacology Reviewer, OCPB, DCPB4
          Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, OCPB, DCPB4

NDA: 22-018

Drug: Lamivudine/Zidovudine Tablets

Subject: Information Request

The following recommendation is being conveyed on behalf of our Clinical Pharmacology Review Team.

Please explain the following discrepancies between the concentrations and/or PK parameters. Further, please recalculate the pharmacokinetic and bioequivalence statistics (point estimates and confidence intervals) based on the updated AUC estimate.

Lamivudine Test Formulation

- For subject 21, the concentration at 36 hours reported in this NDA (b) (4) are different, however, the AUC estimates are identical.

- For subject 25, the concentrations reported in this NDA (b) (4) are identical, however, the AUC estimates are different.
Lamivudine Reference Formulation

- For subjects 16, 23, and 24, the concentrations reported in this NDA (b)(4) are different; however, the AUC estimates are identical. Also, please explain the discrepancy between the concentrations for subject 16.

If you have any questions, please contact me at 301-796-0793 or via email at Vasavi.reddy@fda.hhs.gov

Thank you,

Vasavi Reddy

Vasavi T. Reddy, R.Ph., MPH, LCDR., USPHS
Sr Program Management Officer Consultant, DAVDP
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/s/
---------------------
Vasavi Reddy
7/5/2006 02:54:03 PM
CSO

Kellie Reynolds
7/7/2006 12:24:02 PM
BIOPHARMACEUTICS
NDA 22-018

Pharmacare Ltd.
Attention: Lorraine Hill
Building 12
Healthcare Park
Woodlands Dr
Woodmead, Johannesburg, 2158
South Africa

Dear Ms.Hill:

Please refer to your New Drug Application (NDA) 22-018 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lamivudine 150mg/Zidovudine 300mg fixed dose tablets.

We also refer to your request for fast track designation dated February 18, 2006 received on February 24, 2006.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Lamivudine 150mg/Zidovudine 300mg fixed dose tablets for treatment of HIV infection as a fast track product. Please note, FDA will not consider approval of the brand name "[redacted]" under the Tentative Approval process. This application will be considered under the product name lamivudine 150 mg/zidovudine 300 mg. If you wish to market this application in the U.S. once the period of patent and exclusivity has expired you are encouraged to submit your proposal for the brand name "[redacted]" for FDA’s consideration at least 180 days prior to the period of patent and exclusivity expiration.

We are granting fast track designation for the following reasons:

This application is being submitted in response to the May 2004 draft Guidance for Industry, “Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV.” This guidance was developed to encourage the development and approval of fixed dose combination and co-packaged versions of previously approved antiretroviral therapies, so that these products are available for the treatment and prevention of the global spread of HIV/AIDS. Swift evaluation of the safety, efficacy, and quality of these products is vital if the President’s Emergency Plan for AIDS Relief is to effectively address this urgent public health need.
If you have any questions, contact Vasavi Reddy, RPh, MPH, Regulatory Project Manager, at 301-796-0793 or via email at reddyv@cdr.fda.gov.

Sincerely,

{See appended electronic signature page}

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

CC: Keith Guinta
U.S. Agent for Pharmacare Ltd.
76 South Orange Ave
Suite #203
South Orange, NJ 07079
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/s/

---------------------
Jeffrey Murray
3/29/2006 01:23:09 PM
# NDA/Efficacy Supplement Action Package Checklist

## Application Information

<table>
<thead>
<tr>
<th>NDA 22-018</th>
<th>Efficacy Supplement Type</th>
<th>Supplement Number</th>
</tr>
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<tbody>
<tr>
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<td>SE-</td>
<td></td>
</tr>
</tbody>
</table>

**Drug:** Lamivudine/Zidovudine 150 mg/300mg Tablets  
**Applicant:** Pharmacare Limited  
**RPM:** Vasavi Reddy, R.Ph., M.P.H.  
**Division of Antiviral Products**  
**Phone # 301-796-0793**

Application Type:  
1. ( ) 505(b)(1)  
2. (*) 505(b)(2)  
(This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.

( ) Confirmed and/or corrected

### Application Classifications:

- **Review priority**  
  - ( ) Standard  
  - (*) Priority  
- **Chem class (NDAs only)**  
  - Type IV  
- **Other (e.g., orphan, OTC)**

### User Fee Goal Dates

- **Priority**  
  - ( ) None  
  - Subpart H  
    - ( ) 21 CFR 314.510 (accelerated approval)  
    - ( ) 21 CFR 314.520 (restricted distribution)  
  - (*) Fast Track  
  - ( ) Rolling Review  
  - ( ) CMA Pilot 1  
  - ( ) CMA Pilot 2

### User Fee Information

- **User Fee**  
  - ( ) Paid  
  - UF ID number

- **User Fee waiver**  
  - ( ) Small business  
  - ( ) Public health  
  - (*) Barrier-to-Innovation  
  - ( ) Other (specify)

- **User Fee exception**  
  - ( ) Orphan designation  
  - ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions)  
  - ( ) Other (specify)

### Application Integrity Policy (AIP)

- **Applicant is on the AIP**  
  - ( ) Yes  
  - ( ) No

---

This application is on the AIP

Exception for review (Center Director’s memo)  

OC clearance for approval  

Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are assigned by US agent.

<table>
<thead>
<tr>
<th>Patent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information: Verify that Form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</td>
</tr>
<tr>
<td>Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</td>
</tr>
<tr>
<td>[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</td>
</tr>
<tr>
<td>[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next box below (Exclusivity)).</td>
</tr>
<tr>
<td>[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:</td>
</tr>
<tr>
<td>Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?</td>
</tr>
<tr>
<td>(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))).</td>
</tr>
<tr>
<td>If “Yes,” skip to question (4) below. If “No,” continue with question (2).</td>
</tr>
<tr>
<td>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)?</td>
</tr>
<tr>
<td>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 box below (Exclusivity).</td>
</tr>
<tr>
<td>If “No,” continue with question (3).</td>
</tr>
<tr>
<td>Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</td>
</tr>
</tbody>
</table>
| (Note: This can be determined by confirming whether the Division has received a written notice from the 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.

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)?

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 box below (Exclusivity).

If “No,” continue with question (5).

Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner’s receipt of the applicant’s notice of certification?

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 within the 45-day period).

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 box below (Exclusivity).

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.

Exclusivity (approvals only)

Exclusivity summary

Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

No

Is there existing orphan drug exclusivity protection for the “same drug” for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

() Yes, Application #__________

() No

Administrative Reviews (Project Manager, ADRA) (indicate date of each review)
## General Information

<table>
<thead>
<tr>
<th>Actions</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Proposed action</td>
<td>( ) AP  (✔) TA  ( ) AE  ( ) NA</td>
</tr>
<tr>
<td>Previous actions (specify type and date for each action taken)</td>
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</tr>
<tr>
<td>Status of advertising (approvals only)</td>
<td>N/A</td>
</tr>
<tr>
<td>Materials requested in AP letter</td>
<td>( )</td>
</tr>
<tr>
<td>Reviewed for Subpart H</td>
<td></td>
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</tbody>
</table>

| Public communications |  |
| Press Office notified of action (approval only) | (✔) Yes  (✔) Not applicable |
| Indicate what types (if any) of information dissemination are anticipated | ( ) None  ( ) Press Release  ( ) Talk Paper  ( ) Dear Health Care Professional Letter |

<table>
<thead>
<tr>
<th>Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</th>
<th></th>
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<tbody>
<tr>
<td>Division’s proposed labeling (only if generated after latest applicant submission of labeling)</td>
<td>N/A</td>
</tr>
<tr>
<td>Most recent applicant-proposed labeling</td>
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<tr>
<td>Original applicant-proposed labeling</td>
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</tr>
<tr>
<td>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<em>indicate dates of reviews and meetings</em>)</td>
<td>N/A</td>
</tr>
<tr>
<td>Other relevant labeling (e.g., most recent 3 in class, class labeling)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

| Labels (immediate container & carton labels) |  |
| Division proposed (only if generated after latest applicant submission) | Included |
| Applicant proposed | Included |
| Reviews | See CMC |

| Post-marketing commitments |  |
| Agency request for post-marketing commitments | N/A—Tentatively Approved Application (PEPFAR) |
| Documentation of discussions and/or agreements relating to post-marketing commitments | N/A |
| Outgoing correspondence (i.e., letters, E-mails, faxes) | Included |
| Memoranda and Telecons | Included |

| Minutes of Meetings |  |
| EOP2 meeting (indicate date) | N/A |
| Pre-NDA meeting (indicate date) | N/A |
| Pre-Approval Safety Conference (indicate date; approvals only) | N/A |
| Other |  |

| Advisory Committee Meeting |  |
| Date of Meeting | N/A |
| 48-hour alert | N/A |
| Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | N/A |

# Summary Application Review

- **Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)** *(indicate date for each review)*  
  Included August 23, 2006

## Clinical Information

- **Clinical review(s)** *(indicate date for each review)*  
  Included-Div Dir Memo August 23, 2006

- **Microbiology (efficacy) review(s)** *(indicate date for each review)*  
  N/A

- **Safety Update review(s)** *(indicate date or location if incorporated in another review)*  
  N/A

- **Risk Management Plan review(s)** *(indicate date/location if incorporated in another rev)*  
  N/A

- **Pediatric Page** *(separate page for each indication addressing status of all age groups)*  
  Included

- **Demographic Worksheet** *(NME approvals only)*  
  N/A

- **Statistical review(s)** *(indicate date for each review)*  
  N/A

- **Biopharmaceutical review(s)** *(indicate date for each review)*  
  Included August 9, 2006

- **Controlled Substance Staff review(s) and recommendation for scheduling** *(indicate date for each review)*  
  N/A

- **Clinical Inspection Review Summary (DSI)**  
  - Clinical studies  
    N/A
  - Bioequivalence studies  
    N/A

## CMC Information

- **CMC review(s)** *(indicate date for each review)*  
  Included August 18, 2006

**Environmental Assessment**

- **Categorical Exclusion** *(indicate review date)*

- **Review & FONSI** *(indicate date of review)*

- **Review & Environmental Impact Statement** *(indicate date of each review)*

- **Microbiology (validation of sterilization & product sterility) review(s)** *(indicate date for each review)*  
  Date completed:  
  (✓) Acceptable  
  () Withhold recommendation

- **Facilities inspection** *(provide EER report)*  
  (✓) Completed  
  () Requested  
  () Not yet requested

## Nonclinical Pharm/Tox Information

- **Pharm/tox review(s), including referenced IND reviews** *(indicate date for each review)*  
  N/A

- **Nonclinical inspection review summary**

- **Statistical review(s) of carcinogenicity studies** *(indicate date for each review)*

- **CAC/ECAC report**
Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- it relies on the Agency's previous approval of another sponsor’s drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean any reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Monica Zeballos
8/24/2006 08:49:18 AM
RE: NDA 22-018, Pharmacare Limited, Fixed Dose Combination Tablets of Lamivudine and Zidovudine, Fiscal Year 2006 Application Fee Waiver Request 2006.036

Dear Mr. Giunta:

This responds to your February 2, 2006, and February 16, 2006, letters on behalf of Pharmacare Limited (Pharmacare), requesting a waiver of user fees under the public health and barrier-to-innovation waiver provisions, sections 736(d)(1)(A) and (B)¹ of the Federal Food, Drug, and Cosmetic Act (the Act) (waiver request 2006.036). You requested a waiver of the fiscal year (FY) 2006² application fee for new drug application (NDA) 22-018 for a fixed dose combination (FDC) lamivudine and zidovudine tablet, 150 mg/300 mg.³

For the reasons described below, the Food and Drug Administration (FDA) grants the request of Pharmacare for a barrier-to-innovation waiver of the FY 2006 application fee for NDA 22-018, FDC lamivudine and zidovudine tablets. Because the waiver is granted under the barrier-to-innovation waiver provision, it is not necessary to address the waiver request under the public health waiver provision.

1. Pharmacare’s Request

According to your request for a waiver of user fees, your NDA will be for an FDC antiretroviral product in accordance with FDA’s May 2004 draft guidance for industry on Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV (HIV).

¹ 21 U.S.C. 379h(d)(1)(A) and (B).
³ You requested a waiver of “any and all” user fees based on public health and barrier-to-innovation criteria. This response is valid only for the application fee for NDA 22-018. Currently, Pharmacare has not been assessed product and establishment (P&E) fees, nor is it the Food and Drug Administration’s plan to assess P&E fees to Pharmacare until your application is fully approved. The Agency does not assess P&E fees for applications that have a tentative approval. Therefore, it is not necessary for FDA to act on a waiver request for P&E fees. If Pharmacare is assessed P&E fees, you may submit a new waiver request no later than 180 days after payment of the P&E fees is due.
guidance). You state that FDC lamivudine and zidovudine will be made available for procurement at competitive prices under the President’s Emergency Plan for AIDS Relief (PEPFAR). You state that the product registration has recently been submitted for approval in:

You further state that these products will be an innovative benefit to the public health because they will simplify distribution, improve patient compliance, and have a significant impact on global efforts to treat HIV.

Pharmacare requests that tentative approval be granted as soon as possible so that it can immediately manufacture the products for the PEPFAR program. Further, you state that Pharmacare has obtained, and will abide by, a right of reference agreement with GlaxoSmithKline, and will submit the application as a 505(b)(2) application. Finally, you describe the corporate structure of the Aspen Pharmacare group of companies and cite total annual revenues through June 2005 of approximately $8

II. Criteria for Barrier-to-Innovation Waivers

A. What are the criteria for a barrier-to-innovation waiver?

Under the Act, a waiver or reduction of fees may be granted if the assessment of the fees would present a significant barrier to innovation because of limited resources available to the applicant or other circumstances (section 736(d)(1)(B)). As FDA has interpreted this provision, a waiver or reduction may be appropriate when (1) the product for which the waiver is being requested is innovative or the entity requesting the waiver is otherwise pursuing innovative drug products or technology and (2) the fee would be a significant barrier to the entity’s ability to develop, manufacture, or market innovative products or technology.

B. What other factors are considered when determining whether a product is innovative?

A product that has been approved for marketing in the United States is not automatically deemed to be a product that is innovative within the meaning of the Act. In evaluating whether a drug product is innovative for these purposes, FDA considers, among other factors, whether a drug product is a new molecular entity, has been designated as a priority drug, or has been granted fast track status. We will also consider the existence of treatment alternatives. The existence of treatment alternatives will weigh against deciding that a product is innovative.

1 Available on the Internet at www.fda.gov/cedar/guidance.


3 Further information regarding fast track status can be found in FDA’s guidance for industry on Fast Track Drug Development Programs—Designation, Development, and Application Review, available on the Internet at www.fda.gov/cedar/guidance.
III. Evaluation of Pharmacaecre's Waiver Request

To qualify for a waiver under the barrier-to-innovation waiver provision, you must meet both criteria under that waiver provision.

A. Is Pharmacaecre’s FDC of Lamivudine and Zidovudine innovative?

In the HIV guidance, FDA encouraged sponsors to submit certain applications for co-packaged HIV products. We have confirmed that your product is on the list of examples in Attachment B of the HIV guidance. Because each active ingredient was previously approved, your product will not be considered a new molecular entity. However, the application has been identified for a priority review and will be given a fast track designation. FDA also considers that the products listed in Attachment B to the HIV guidance are innovative, because such simplified regimens that will facilitate distribution and patient compliance, particularly in treatment-naive patients, are needed in developing countries. Considering all the factors noted above, FDA finds that Pharmacaecre’s FDC lamivudine and zidovudine tablets is a product that, for user fee waiver purposes, is innovative.7

B. Is the fee a significant barrier to the entity’s ability to develop, manufacture, or market innovative products?

In evaluating whether the application fee imposed is a significant barrier to the entity’s ability to develop, manufacture, or market innovative products, the Agency considers the relationship between the annualized cost of user fees and the total annual revenue of the entity requesting the waiver and its affiliates.8 This consideration is discussed in FDA’s waiver guidance.9

In your waiver requests, you specified that the total revenues for the year ending June 2005 for Pharmacaecre and its affiliates were approximately $________ (U.S.). In light of the evidence of Pharmacaecre’s total annual revenue and based on the waiver guidance,

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7 Attachment B includes the two-drug regimen of lamivudine and zidovudine proposed in your product.
8 Please refer to FDA’s April 2005 draft guidance for industry on User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR (PEPFAR waiver guidance), available on the Internet at www.fda.gov/center/guidance, for a full discussion on why FDA currently considers fixed dose combinations or co-packaged products for the treatment of HIV to be innovative.
9 Please note that after several alternative treatments have been made available, FDA may reevaluate whether these products remain innovative and may find that, because of the existence of treatment alternatives, user fee waivers may no longer be appropriate.
10 Section 103(b) of the Food and Drug Administration Modernization Act of 1997 (Modernization Act) reaffirms that the person subject to fees “shall continue to include an affiliate thereof.”
12 Pharmacaecre Limited is a member of the Aspen Pharmacaecre group of companies. The group includes Pharmacaecre Limited, and Aspen Pharmacaecre.
FDA concludes that Pharmacare is a Type 2 pharmaceutical firm (parent corporation has gross annual revenue between $\text{[redacted]}^{(b)}$). FDA believes that an entity with more than $10 million in annual gross revenue is generally able to develop, manufacture, or market innovative products or technology without a waiver.\textsuperscript{13} Ordinarily, FDA would conclude that the application fee would not present a significant barrier to Pharmacare’s ability to develop, manufacture, or market innovative products or technology, and would deny Pharmacare’s waiver request.

Under section 736(d)(1)(B) of the statute, however, FDA may consider circumstances other than limited resources when evaluating a barrier-to-innovation waiver request, and has decided to do so in this case.\textsuperscript{14} As previously indicated, FDA issued the HIV guidance in May 2004 to encourage applicants to submit applications for HIV combination therapies that can be used in PEPFAR.

According to the information you provided and confirmed by the FDA Division of Anti-Viral Products:

- You are submitting a 505(b)(2) application for an FDC of lamivudine and zidovudine tablets for treatment of HIV from among the examples listed in Attachment B of the HIV guidance.\textsuperscript{15}

- You are obtaining tentative approval for your products in the United States, and you intend to make your products available to PEPFAR at competitive prices.

- You provided a plan and schedule for the submission of an application for approval in one or more of the PEPFAR countries.\textsuperscript{16}

Consequently, considering all the relevant factors, your request for a barrier-to-innovation waiver of the FY 2006 application fee for NDA 22-018 for an FDC of lamivudine and zidovudine tablets, 150 mg/300 mg, is granted, provided your application is received within 1 year of the date of this letter and it is a 505(b)(2) application. Please include a copy of this letter with your application. We have notified the Office of Financial Management of this waiver decision and have asked them to waive the application fee for Pharmacare’s NDA 22-018 for fixed dose combination tablets of lamivudine and zidovudine 150 mg/300 mg.

If FDA refuses to file the application or Pharmacare withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should Pharmacare resubmit its marketing application. If this situation occurs, Pharmacare should contact this office.

\textsuperscript{13} Waiver guidance at page 17.

\textsuperscript{14} See pages 4 and 5 of the PEPFAR waiver guidance for a discussion of “other circumstances.”

\textsuperscript{15} This decision on your waiver request should not be construed as a decision on whether your application is properly submitted as a 505(b)(2) application.

\textsuperscript{16} Specifically, you noted that you have recently submitted for approval lamivudine and zidovudine tablets applications in many PEPFAR countries (see section 1 above).
approximately 45 days before the company expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

IV. Disclosure of Public Information

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If you have any questions about this matter, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research
cc:
HFD-5, M.Jones
HFD-5, Chron. File
HFD-5, Pharmacare Waiver File NDA 22-018
HFD-7, B. Friedman/T. Schwemer/E. Thakur/M. Nguyen
HFD-530, V. Reddy
HFM-110, C. Vincent/R. Eastep
HFA-100 M. Louviere
HFA-120 P. Joseph/K. Boyd (waiver granted)
HF-20, F. Claunts
HVM-3, T. Forfa
HVM-100, D. Newkirk
GCF-1, L. Mehler-Whipkey, K. Fain

drafted 2/22/2006, M.Jones
comments 2/23/2006 B. Friedman
revised 2/24/2006 M.Jones
edited 2/27/2006 S. O'Malley
revised 2/28/2006 M. Jones
comments 3/2/06 J. Axelrad
revised 3/6/06 M. Jones

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