

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022018Orig1s000

OTHER REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Division of Antiviral Products
Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993**

Clinical Labeling Review

Date	March 13, 2017
From	Monica Zeballos, Pharm.D. Program Coordinator Division of Antiviral Products (DAVP)
Through	Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP
NDA # Supplement #	1) 22018-SUPPL-2 Labeling 2) 22018-ORIG-1-RESUB-16
Original Regulatory Action and Date	Tentative Approval (TA) on 23Aug2006 PEPFAR
Applicant	Pharmacare Limited t/a Aspen Pharmacare, South Africa
U.S. Agent	Lachman Consultants Services Inc. Attention: Diana Slone, Senior Associate
Letter Date	1) March 17, 2015 2) Sept 17, 2016
Stamp Date	1) March 19, 2015 2) Sept 19, 2016
Goal Date	1) Sept 19, 2015 2) March 19, 2017
Established Name	Lamivudine and Zidovudine
Dosage Form/Strength	Tablets, 150 mg/300 mg
Subject	1) PLR conversion of PI 2) Class 2 Resubmission to a TA Requesting Final Approval After All Listed Patents for COMBIVIR Expired on 18Nov2016
Materials Reviewed	➤ Electronic NDA/S-002 and NDA/Resubmission to a TA ➤ U.S. labeling for COMBIVIR (lamivudine and zidovudine) tablets, 150 mg/300 mg approved on 24Feb2017 under NDA 20857 ➤ OSE/DMEPA Review of the PI & Container/Carton Labels ➤ OMP/OPDP Review of the PI & Container/Carton Labels ➤ OPQ Labeling Recommendations for the PI
Recommended	1) Permitted 2) Approval

I. Background

Pharmacare Limited's (also known as Aspen Pharmacare) original 505(b)(2) NDA 22018 was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR) and granted tentative approval on 23Aug2006. (b) (4)

Pharmacare Limited's product is (b) (4) unscored, which supports DAVP's current recommendation of this product for final approval and complies with the "Tablet Scoring" guidance, and COMBIVIR's is scored. (b) (4)

In addition, DAVP made the administrative decision in 20016 to review Pharmacare Limited's 2-drug fixed-dose combination NDA as a 505(2) (b) (4)

On March 17, 2015, Pharmacare Limited submitted a labeling amendment for the PLR (Physician's Labeling Rule) conversion of the package insert (PI). This memo will also address the labeling amendment and will close out the pending internal goal date for 22018/SUPPL-2 in lieu of a "PEPFAR Permitted" letter.

On Sept 17, 2016, Pharmacare Limited submitted a class 2 resubmission to a TA to gain final approval and marketing in the United States after all the listed patents for COMBIVIR expired on 18Nov2016.

II. Labeling Review

All sections of the PI in PLR format for this 2-drug fixed-dose combination product were reviewed and compared to the latest approved U.S. labeling for COMBIVIR. Additionally, all the labeling recommendations for the PI from OPQ and OSE/DMEPA (Division of Medication Error Prevention and Analysis) have been annotated in the PI, which is attached at the end of this memo. OPDP (Office of Prescription Drug Promotion) have no comments for the PI or container/carton labels.

The content and format of the proposed PI is similar to the U.S. labeling for COMBIVIR. Notable differences include:

1. HIGHLIGHTS section: For reporting suspected Adverse Reaction, Pharmacare Ltd. provided the following U.S. phone number:
 - **To report SUSPECTED ADVERSE REACTIONS, contact Aspen Pharmacare at 1-855-800-8165 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**
2. Pharmacare Limited has provided proof that it has joined the Antiretroviral Pregnancy Registry.
3. There were no new bioequivalence (BE) studies for this NDA. The results of a BE study under fasted conditions were previously submitted (b) (4)

Because BE was only assessed under fasting conditions, this product must be administered on an empty stomach. In summary, DAVP made reference (b) (4) because it had already reviewed the lamivudine and zidovudine tablet BE data.

4. Important information from COMBIVIR relevant to the use of this product and recommendations from OPQ and OSE/DMEPA were added to the USE IN SPECIFIC POPULATIONS (8.1, 8.2), NONCLINICAL TOXICOLOGY (13.1), HOW SUPPLIED/STORAGE AND HANDLING (16), and PATIENT COUNSELING INFORMATION (17) sections as follows:
 - Subsections 8.1 and 8.2: Updated according to the Pregnancy and Lactation Labeling Rule
 - Subsection 13.1: Updated impairment of fertility information
 - Section 16: Per OPQ's recommendations, updated the storage statement based on demonstrated stability and in consideration of the USP Monograph and how supplied information
 - Section 17: Updated/added information on lactic acidosis/hepatomegaly with steatosis, drug interactions, immune reconstitution syndrome, pregnancy registry, lactation, and missed dose (OSE/DMEPA's recommendations were for the Lactation and Missed dose)

III. Recommended Regulatory Action

The proposed PI was reviewed and should allow for the safe and effective use of this fixed-dose combination product. Pharmicare Ltd. has adequately responded to the Division's labeling revisions for the PI conveyed on March 14, 2017, via email correspondence; therefore, an approval action is warranted.

Monica Zeballos, Pharm.D.
Program Coordinator
Division of Antiviral Products
Office of Antimicrobial Products

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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
03/15/2017

JEFFREY S MURRAY
03/16/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 22018	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: NA Established/Proper Name: Lamivudine and Zidovudine Dosage Form: Tablets Strengths: 150 mg/300 mg		
Applicant: Pharmacare Limited, South Africa		
Date of Receipt: 19Sept2016. This is a class 2 resubmission after a TA action requesting final approval after all the listed drug patents/exclusivities expired for COMBIVIR		
PDUFA Goal Date: Sunday, 19March2017	Action Goal Date (if different): Friday, 17March2017	
RPM: Monica Zeballos		
Proposed Indication(s): Treatment of HIV-1 infection in combination with other antiretroviral		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 20857 COMBIVIR (lamivudine and zidovudine) tablets	FDA's previous finding of safety and effectiveness (e.g., clinical or nonclinical or both)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

In vivo bioequivalence (BE) studies comparing lamivudine and zidovudine to COMBIVIR were performed and these studies were found acceptable/adequate by OCPB (Office of Clinical Pharmacology and Biopharmaceutics) and DSI (Division of Scientific Investigations). However, there were no new BE studies for this NDA. The results of a BE study under fasted conditions were previously submitted (b) (4)

Because BE was only assessed under fasting conditions, this product must be administered on an empty stomach. In summary, DAVP made reference (b) (4) **because it had already reviewed the lamivudine and zidovudine tablet BE data.**

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO
If "NO," proceed to question #5.

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
COMBIVIR (lamivudine and zidovudine) tablets, 150 mg/300 mg	20857	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Pharmacare Limited's (also known as Aspen Pharmacare) original 505(b)(2) NDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR) and granted tentative approval on 23Aug2006. (b) (4)

Pharmacare Limited's product is (b) (4) unscored, which supports DAVP's current recommendation of this product for final approval and complies with the "Tablet Scoring" guidance, and COMBIVIR's is scored. (b) (4)

In addition, DAVP (b) (4) review Pharmacare Limited's 2-drug fixed-dose combination NDA as a 505(2) (b) (4)

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to

FDA. (Paragraph I certification)

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): **5905082*PED**

Expiry date(s): **Nov 18, 2016**

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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
03/15/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 13, 2017
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 22018
Product Name and Strength: Lamivudine and Zidovudine Tablets,
150 mg/300 mg
Product Type: Multi-ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Pharmicare Limited (LTD)
Submission Date: September 17, 2016
OSE RCM #: 2017-492
DMEPA Primary Reviewer: Valerie Wilson, PharmD
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Pharmacare Limited (LTD) submitted a 505b(2) New Drug Application (NDA 22018), that was amended under President's Emergency Plan for AIDS Relief (PEPFAR) and tentatively approved on August 23, 2006. On September 19, 2016, Pharmacare LTD submitted a class 2 resubmission requesting final approval and included proposed labels and labeling for Lamivudine and Zidovudine tablets.

DAVP intends to send the following four revisions for the proposed Lamivudine and Zidovudine prescribing information (PI):

- 1) *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"*
- 2) *Please revise the name of the product on the bottle label and throughout the prescribing information to read: "Lamivudine and Zidovudine Tablets"*
- 3) *Please modify the list of inactive ingredients in Section 10 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 glycolate, and talc"*
- 4) *Please modify the statement in Section 16 to read: "60 Tablets/Bottle with desiccant, induction seal and child-resistant cap (NDC 52719-760-59)"*

and requests we review the edits on track changes in the PI (Appendix G), along with the proposed carton and container labels, to determine if areas of vulnerability to medication errors are present.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Lamivudine and Zidovudine Tablet is proposed for use in adults, adolescents weighing greater than or equal to 30 kg, and pediatrics who weigh greater than or equal to 30 kg and for whom a solid oral dosage form is appropriate. Lamivudine and Zidovudine Tablets will be supplied in bottles of 60 tablets to support a twice-daily dosing regimen.

We agree with DAVP’s proposed revisions stated in Section 1. Our assessment of the Dosage and Administration, Dosage Forms and Strengths, How Supplied/Storage and Handling, Patient Counseling, and Patient Information sections of the full prescribing information (FPI), container label, and carton labeling identified the following deficiency and discrepancy that could lead to medication errors.

Container Label

Our assessment of the container label identified that an area for the expiration date has not been designated on the container label. To prevent medication errors relating to administration of expired medication the expiration date is required on the immediate container label per 21 CFR 201.17. Additionally, we note an area for the lot number has not been designated but is required to appear on the immediate container label per 21 CFR 201.10(i)(1).

Prescribing Information

Our assessment of the prescribing information revealed that important patient counseling information about lactation and missed doses does not appear in the same readable manner as in the Combivir PI. We are concerned this important information in Section 17 (Patient Counseling Information) of the Lamivudine and Zidovudine Tablet PI could be missed, as the information is not clearly separated out. We recommend the patient counseling information about lactation and missed doses is placed under their own headings “Lactation” and “Missed Dose,” respectively.

4 CONCLUSION & RECOMMENDATIONS

Our review of the container label, carton labeling, and prescribing information determined the container label and prescribing information require revision. We provide our recommendation to the Division in section 4.1 and our recommendation in letter-ready format to the Applicant in section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. We recommend important patient counseling information pertaining to lactation and missed doses is placed under their own headings (i.e. Lactation and Missed Dose) in section 17 (Patient Counseling Information) so this information is not inadvertently missed.

4.2 RECOMMENDATIONS FOR PHARMACARE LTD

We recommend the following be implemented prior to approval of this NDA:

1. Add the lot number and expiration date to the immediate container label per 21 CFR 201.10(i)(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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lamivudine and Zidovudine Tablets that Pharmacare LTD submitted on September 19, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Lamivudine and Zidovudine Tablets and the Listed Drug		
Product Name	Lamivudine and Zidovudine Tablets	Combivir
Initial Approval Date	Tentatively approved August 23, 2006	September 26, 1997
Active Ingredient	lamivudine and zidovudine	lamivudine and zidovudine
Indication	Lamivudine and Zidovudine Tablets, a combination of 2 nucleoside analogues, is indicated in combination with other antiretrovirals for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.	COMBIVIR, a combination of 2 nucleoside analogues, is indicated in combination with other antiretrovirals for the treatment of human immunodeficiency virus type 1 (HIV 1) infection.
Route of Administration	Oral	Oral
Dosage Form	Tablets	Tablets
Strength	150 mg/300 mg	150 mg/300 mg
Dose and Frequency	Adults, adolescents weighing greater than or equal to 30 kg, peditrics who weigh greater than or equal to 30 kg and for whom solid oral dosage form is appropriate: 1 tablet twice daily	Adults, adolescents weighing greater than or equal to 30 kg, peditrics who weigh greater than or equal to 30 kg and for whom solid oral dosage form is appropriate: 1 tablet twice daily
How Supplied	Bottles of 60 (NDC 52719-760-59)	Bottles of 60 (NDC 49702-202-18) Unit Dose Pack of 120 (NDC 49702-202-29)
Storage	20° to 25°C (68° to 77°F), (see USP Controlled Room Temperature). Protect from moisture and light.	Store between 2° and 30°C (36° and 86°F).
Container Closure	Not provided	Not provided

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Lamivudine and Zidovudine Tablets label and labeling submitted by Pharmicare Limited on September 19, 2016.

- Container label
- Carton labeling
- Prescribing Information

G.2 Label and Labeling (Images)

Container Label



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

VALERIE S WILSON
03/13/2017

BRENDA V BORDERS-HEMPHILL
03/13/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 13, 2017

To: Monica Zeballos, PharmD, Regulatory Project Manager
Division of Antiviral Products

From: Wendy Lubarsky, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: NDA 022018 - LAMIVUDINE AND ZIDOVUDINE TABLETS, 150 mg/300 mg

As requested in the Division of Antiviral Products' (DAVP) consult dated March 9, 2017, the Office of Prescription Drug Promotion (OPDP) has reviewed the LAMIVUDINE AND ZIDOVUDINE TABLETS, 150 mg/300 mg proposed prescribing information (PI), only taking into account the labeling revisions listed in the consult request form, and the proposed edits to the PI in track changes on pages 1 and 2, and the carton/container labeling.

OPDP reviewed the proposed substantially complete versions of the PI and carton/container labeling sent via email on March 9, 2017, and has no comments at this time.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WENDY R LUBARSKY
03/13/2017