CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-294

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

AUROBINDO

29th November 2007

Patent Certification

Paragraph II Certification

In accordance with the Federal Food, Drug and Cosmetic Act (FDCA), as amended December 8, 2003 (Prescription Drugs and Medicare Improvement Act of 2003), and with the Code of Federal Regulation as amended and effective April 08, 2004, Patent Certification is hereby provided for our New Drug Application (NDA) for Zidovudine Tablets USP 60mg. This certification is made in accordance with Section 505 (b)(2) of Title I of the Food, Drug and Cosmetic Act and pursuant to 21 CFR 314.50 (i)(1)(i)(A)(2).

According to the information published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), Aurobindo hereby certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 4,724,232, held by Burroughs Wellcome Inc., and listed for the Reference Listed Drug **RETROVIR® (zidovudine) Tablets 300mg** has expired on September 17, 2005.

for **APL RESEARCH CENTRE**
(A Division of Aurobindo Pharma Limited)

Handa

Dr. V. K. Handa
President

APL RESEARCH CENTRE
(A Division of Aurobindo Pharma Ltd)
313, Bachupally, Quthubullapur (Mandal), RR District, Hyderabad - 500 072 A.P., INDIA. Tel : + +91 40 2304 0261, Fax : + +91 40 2304 2932
Regd. Off. : Plot No. 2, Maitrivihar, Ameerpet, Hyderabad - 500 038 A.P., INDIA. Tel : + + 91 40 6672 5000, Fax : + + 91 40 2374 6833, 2374 1080

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According to the information published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), Aurobindo hereby certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 4,818,538, held by Burroughs Wellcome Inc., and listed for the Reference Listed Drug **RETROVIR® (zidovudine) Tablets 300mg** has expired on September 17, 2005.

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29th November 2007

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According to the information published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), Aurobindo hereby certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 4,828,838, held by Burroughs Wellcome Inc., and listed for the Reference Listed Drug **RETROVIR® (zidovudine) Tablets 300mg** has expired on September 17, 2005.

for **APL RESEARCH CENTRE**
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AUROBINDO

29th November 2007

Patent Certification

Paragraph II Certification

In accordance with the Federal Food, Drug and Cosmetic Act (FDCA), as amended December 8, 2003 (Prescription Drugs and Medicare Improvement Act of 2003), and with the Code of Federal Regulation as amended and effective April 08, 2004, Patent Certification is hereby provided for our New Drug Application (NDA) for Zidovudine Tablets USP 60mg. This certification is made in accordance with Section 505 (b)(2) of Title I of the Food, Drug and Cosmetic Act and pursuant to 21 CFR 314.50 (i)(1)(i)(A)(2).

According to the information published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), Aurobindo hereby certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 4,833,130, held by Burroughs Wellcome Inc., and listed for the Reference Listed Drug **RETROVIR® (zidovudine) Tablets 300mg** has expired on September 17, 2005.

for **APL RESEARCH CENTRE**
(A Division of Aurobindo Pharma Limited)

Dr. V. K. Handa
President

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AUROBINDO

29th November 2007

Patent Certification

Paragraph II Certification

In accordance with the Federal Food, Drug and Cosmetic Act (FDCA), as amended December 8, 2003 (Prescription Drugs and Medicare Improvement Act of 2003), and with the Code of Federal Regulation as amended and effective April 08, 2004, Patent Certification is hereby provided for our New Drug Application (NDA) for Zidovudine Tablets USP 60mg. This certification is made in accordance with Section 505 (b)(2) of Title I of the Food, Drug and Cosmetic Act and pursuant to 21 CFR 314.50 (i)(1)(i)(A)(2).

According to the information published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), Aurobindo hereby certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 4,837,280, held by Burroughs Wellcome Inc., and listed for the Reference Listed Drug **RETROVIR® (zidovudine) Tablets 300mg** has expired on September 17, 2005.

for **APL RESEARCH CENTRE**
(A Division of Aurobindo Pharma Limited)

Handa

Dr. V. K. Handa
President

AUROBINDO

29th November 2007

Exclusivity Certification

Aurobindo hereby certifies that based on the information published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), the Reference Listed drug **RETROVIR® (zidovudine) Tablets 300mg** is not covered by any type of exclusivity as on date.

The Orange Book Listing for this exclusivity is enclosed in this module 1.3.5.1 for ready reference.

For **APL RESEARCH CENTRE**
(A Division of Aurobindo Pharma Limited)

Handa
Dr. V. K. Handa
President

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(A Division of Aurobindo Pharma Ltd)
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PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: **22-294** Supplement Number: **NA** NDA Supplement Type (e.g. SE5): **NA**

Division Name: **DAVP** PDUFA Goal Date: **08/07/09** Stamp Date: **10/07/2008**

Proprietary Name: **Not applicable because it will not be marketed in the United States**

Established/Generic Name: **Zidovudine**

Dosage Form: **Scored Tablets, 60 mg**

Applicant/Sponsor: **Aurobindo Pharma Ltd.**

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) **Treatment of HIV-1 Infection**
(2)
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of HIV-1 Infection

Q1: Is this application in response to a PREA PMC/PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC/PMR #:_____

Does the division agree that this is a complete response to the PMC/PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

Note: On 03June09, the review team met with the PeRC to discuss this application. The PeRC reviewed the following documents for this appropriately labeled application for Zidovudine scored 60mg tablet that dissolves or disperses in water:

- **Partial waiver for pediatric patients weighing less that 4kg or who are less than 6 weeks of age, including draft language to include in the package insert**
- **Pediatric page (review team noted that PREA was triggered as a new dosage form)**
- **Proposed PLR package insert with preliminary review team's revisions**
- **PREA language for approval letter**

During the meeting, one committee member stated the proposed scored 60mg tablet that disperses in water was not considered a new dosage form because there is an adult Retrovir 300 mg tablet already. A chemistry member was not present at the meeting and the final decision regarding PREA was deferred until further discussion within PeRC. On July 16, 2009, Mr. George Greeley, PeRC Project Manager, sent me an email correspondence stating that a subsequent review of the product determined a scored 60 mg tablet that dissolves or disperses in water does not trigger PREA as a new dosage form and no additional review of this product is required by the PeRC because there is no PREA trigger.

Mr. Greeley's email correspondence attached. Based on this final PeRC's determination the original pediatric page was revised on July 21, 2009.

Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.

Q3: Does this indication have orphan designation?

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

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

ck subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding ...dy plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	wk. mo.	wk. mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

i. * Other Reason

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	yr. mo.	yr. mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	wk. __ mo.	wk. mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Dosage recommendations by weight have been provided in labeling for patients weighing 4 kg and greater. These recommendations are based on pharmacokinetic analyses indicating that projected exposures are within the ranges of those achieved with known effective and safe pediatric (mg/kg and BSA) and adult doses.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the

product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Monica Zeballos, Pharm.D., Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

ck subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding dy plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan nplate); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

. ..diatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

...itional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

ction F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

AUROBINDO

Dated: 12th December, 2008

Debra Beinkrant, M.D. Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Sir / Madam,

Generic Drug Enforcement Act – Debarment Certification

Reference: Zidovudine Tablets USP 60 mg.

Pursuant to Section 306(k) of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Aurobindo Pharma Limited here by certifies that Aurobindo Pharma Limited did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this New Drug Application (NDA) 505(b)(2).

Yours sincerely

M. Madan Mohan Reddy
Director for Aurobindo Pharma Limited

Yours sincerely

Blessy Johns
US Agent for Aurobindo Pharma Limited

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # **22-294** BLA #	NDA Supplement # **NA** BLA STN #	If NDA, Efficacy Supplement Type: **NA**
Proprietary Name: **NA** Established/Proper Name: **Zidovudine Tablets (scored), 60 mg** Dosage Form: **Tablets**		Applicant: **Aurobindo Pharma Limted** Agent for Applicant (if applicable): **Blessy Johns**
RPM: **Monica Zeballos**		Division: **Division of Antiviral Products**

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):
(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	**NDA 20-518 Retrovir (zidovudine) Tablets, 300 mg** Provide a brief explanation of how this product is different from the listed drug. **This product was submitted under PEPFAR and it's for a scored tablet that dissolves or disperses in water for the pediatric population** ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☒ No changes ☐ Updated Date of check: **08July09** **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	**17August09** **23July09**
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

Application[2] Characteristics	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): **5 (new formulation or new manufacturer). Note: The CMC Review states 4 (new combination) but the review team later determined 5 is the correct classification in this case because of the following reasons:**

- **NDA is eligible for full approval action vs. TA under PEPFAR**
- **Retrovir 300mg tablet exists**
- **PeRC determined this formulation (scored tablet that disperses or dissolves in water) does not trigger PREA as a new dosage form**

☒ Fast Track
☐ Rolling Review
☐ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: **This application was submitted under the President's Emergency Plan for AIDS Relief (PEPFAR) initiative. The applicant committed not to market this product in the U.S. in letter dated December 1, 2007. This letter was submitted to the Office of Regulatory Policy in support of the user fee waiver request. On July 10, 2009, applicant agreed to submit this letter officially to the NDA. A copy of the letter is attached to the NDA Regulatory Filing Review dated 22July09.**

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	**Application did not trigger PREA. See Pediatric page for explanation.**
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] questions in all sections pertain 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-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 ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: 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 ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric 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 ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic. **This is a 505b2 NDA that is not claiming patent for a drug substance, drug product and/or method of use. Therefore, only the appropriate certification was submitted (paragraph II).**
• 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.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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*	☐ N/A (no paragraph IV certification) ☐ Verified

*any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*

- [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:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

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

  ☐ Yes ☐ No

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

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

  ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

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

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

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

  ☐ Yes ☐ No

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

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

  ☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced 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 section below (*Summary Reviews*).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
Copy of this Action Package Checklist[3]	**Included**
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
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) **Approval letter dated 09July09**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	**Included**
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	**Included**
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☐ DRISK ☐ DDMAC ☐ CSS ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	**Not applicable because this product will be marketed outside the United States**
Administrative / Regulatory Documents	
Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	**NDA Regulatory Filing Review dated 22July09**
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	**Included**
❖ Internal memoranda, telecons, etc.	**Included: Review Timeline**
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☒ Not applicable
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	**none**
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None **Deputy Director as the final signature authority will include a signed-off statement in the approval letter.**
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None **Dated 21July09**
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	**02June09**
• Clinical review(s) *(indicate date for each review)*	**15June09**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	**NA because this is a 505b2 NDA**
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	**NA. See NDA Regulatory Filing Review dated 22July09 for explanation.**
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ 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)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☒ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None **See CDTL's memo dated 21July09**
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None **Dated 09July09**
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None **Not needed because a dissolution-biowaiver was granted for this NDA. See ONDQA Biopharmaceutics Review dated 18May09.**
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None **Dated 08June09**
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	☒ Not needed

❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None **ONDQA Biopharmaceutics Review for the dissolution biowaiver dated 18May09**
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**23Sept08**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: **07March08** ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

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

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** 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.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative Documents Section- E

Zeballos, Monica

From: Greeley, George
Sent: Thursday, July 16, 2009 2:56 PM
To: Zeballos, Monica
Cc: Stowe, Ginneh D.
Subject: NDA 22-294

Importance: High

Hi Monica,

The Zidovudine partial waiver and appropriately labeled application was reviewed by the PeRC PREA Subcommittee on June 03, 2009. The Division noted via the pediatric page for this product that PREA was triggered as a new dosage form. A subsequent review of the product determined that a scored 60 mg tablet that dissolves in water does not trigger PREA.

No additional review of this product is required by the PeRC since there is no PREA trigger.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
g #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

AUROBINDO

Dated: July 09, 2009

To

Debra Beinkrant, M.D. Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Sir/Madam,

SUBJECT: U.S. Agent Authorization Letter

REFERENCE No: APL/API/FRD/235

Please find mentioned below are the details of our designated U.S Agent:

Name of the U.S. Agent: Ms. Blessy Johns

Address: Aurobindo Pharma USA, Inc,
2400 Route 130 North, Dayton, NJ 08810
U.S.A

Phone: 732-839-4380 (Direct number)

Fax : 732-355-9940

Cell : 908-240-1822

E-mail: bjohns@aurobindousa.com

Yours sincerely

for **Aurobindo Pharma Limited**

M. Madan Mohan Reddy
Director

APL RESEARCH CENTRE
(A Division of Aurobindo Pharma Ltd)
313, Bachupally, Quthubullapur (Mandal), RR District, Hyderabad - 500 072 A.P., INDIA. Tel : + +91 40 2304 0261, Fax : + +91 40 2304 2932
Regd. Off. : Plot No. 2, Maitrivihar, Ameerpet, Hyderabad - 500 038 A.P., INDIA. Tel : + + 91 40 6672 5000, Fax : + + 91 40 2374 6833, 2374 1080
www.aurobindo.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-294

Aurobindo Pharma USA, Inc.
Attention: Prasada Kambham
U.S. Agent for Aurobindo Pharma Limited
2400 Route 130 North
Dayton, NJ 08810

Dear Mr. Kambham:

Please refer to Aurobindo's New Drug Application (NDA) 22-294 submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for Zidovudine 60 mg Tablets.

We also refer to your request for fast track designation dated December 18, 2007 and received on December 28, 2007.

We reviewed your request and concluded that it meets the criteria for fast track designation. Therefore, we are designating Zidovudine 60 mg Tablets for the treatment of HIV-1 infection as a fast track product.

We are granting fast track designation for the following reasons:

This application is being submitted in response to the October 2006 final Guidance for Industry, "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the 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, please contact David Araojo, Pharm.D., Sr. Program Management Consultant, at (301) 796-0669 or via email at David.Araojo@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, M.D., M.P.H.
Deputy Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Jeffrey Murray
1/18/2008 12:30:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-294

Aurobindo Pharma USA, Inc.
Attention: Blessy Johns, Manager, Regulatory Affairs
U.S. Agent for Aurobindo Pharma Limited
2400 Route 130 North
Dayton, NJ 08810

Dear Ms. Johns:

Please refer to Aurobindo's new drug application (NDA) 22-294 dated October 3, 2008, received on October 7, 2008, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zidovudine Tablets, 60 mg.

We also refer to Aurobindo's submissions dated:

December 18, 2007	April 21, 2008	September 4, 2008
February 15, 2008	June 2, 2008	December 2, 2008
March 11, 2008	June 25, 2008	December 12, 2008
March 17, 2008	August 22, 2008	

We completed our filing review and determined that Aurobindo's application is sufficiently complete to permit a substantive review. This application was considered filed on December 6, 2008, in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is **August 7, 2009**.

At this time, we are notifying you that, we have not identified any **potential** review issues. Please note that our filing review is only a preliminary evaluation of this application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients from birth to less than 6 weeks of age.

We remind you that because of the lapsed exclusivity and patent protection in the United States for Retrovir® (zidovudine) Tablets, 300 mg, this application is eligible for a full **approval** and not a **tentative approval** action. Therefore, you will have to comply with all the requirements associated with a full approval action.

If you have any questions, please call Monica Zeballos, Pharm.D., Sr. Program Consultant, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Jeffrey Murray, M.D., M.P.H.
Deputy Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Email cc: Roopak Sawhney
Regulatory POC for Aurobindo Pharma Limited in India

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/s/

Jeffrey Murray
12/19/2008 02:17:52 PM

MEMORANDUM

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

DATE: August 29, 2008

TO: Blessy Johns, U.S. Agent for Aurobindo Pharma Limited

FROM: Monica Zeballos, Pharm.D., Sr. Program Consultant, Division of Antiviral Products (DAVP)

CONCUR: Stephen Miller, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment 2 (DPA2), Office of New Drug Quality Assessment (ONDQA)
Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA
Balajee Shanmugan, Ph.D., Chemistry Reviewer, DPA2, ONDQA
Ted Chang, Ph.D., Chemistry Reviewer, DPA2, ONDQA
Rao Kambhampati, Ph.D., Chemistry Reviewer, DPA2, ONDQA
George Lunn, Ph.D., Chemistry Reviewer, DAP2, ONDQA
Dorota Matecka, Ph.D., Chemistry Reviewer, DPA2, ONDQA

NDAs: ____ 22-293, 22-294, 22-295, 22-296 and 22-297 b(4)

APPLICANT: Aurobindo Pharma Limited

SUBJECT: Information Request

Please refer to your New Drug Applications (NDAs) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for procurement under the PEPFAR program for the following products:

- _____ b(4)
- NDA 22-293 Abacavir Sulfate 60 mg Tablets
- NDA 22-294 Zidovudine 60 mg Tablets
- NDA 22-295 Abacavir Sulfate/Lamivudine 60 mg/30 mg Tablets
- NDA 22-296 Zidovudine/Lamivudine 60 mg/30 mg Tablets
- NDA 22-297 Efavirenz 100 mg Tablets

The following request is being conveyed on behalf of the Chemistry Review Team. Please respond via email correspondence and send an archival copy of your response to your NDAs.

1. Please provide a written commitment, applicable to yours NDAs listed above, that within 6 months you will demonstrate conformance with the current USP chapter on Residual Solvents <467>.

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

Sincerely yours,

Monica Zeballos, Pharm.D.
USPHS, LCDR
Senior Program Consultant
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug and Evaluation Research

Email cc: Roopak Sawhney
Regulatory POC for Aurobindo Pharma Limited in India

Post-Memo **Note**

On Sept 1, 2008, Aurobindo requested clarification via email whether the written commitment for the compliance with the current USP chapter on Residual Solvents <467> should be 6 months from the tentative approval date or the amendment date.

On Sept 2, 2008, the following response was sent to Aurobindo via email:

As a clarification to our Aug 29 CMC IR, please provide the written commitment to demonstrate conformance with the current USP chapter on Residual Solvents <467> within 6 months from the tentative approval date.

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/s/

Monica Zeballos
9/12/2008 03:00:06 PM
CSO

Monica Zeballos
9/12/2008 03:00:39 PM
CSO

MEMORANDUM

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

DATE:	July 17, 2008
TO:	Blessy Johns, U.S. Agent for Aurobindo Pharma Limited
FROM:	Monica Zeballos, Pharm.D., Sr. Program Consultant, Division of Antiviral Products (DAVP)
CONCUR:	Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP Kim Struble, Pharm.D., Medical Team Leader, DAVP Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
NDAs:	22-294 and 22-296
APPLICANT:	Aurobindo Pharma Limited
DRUGS:	Zidovudine 60mg and Lamivudine/Zidovudine 30 mg/60 mg
SUBJECT:	Information Request

Please refer to your New Drug Applications (NDAs) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for procurement under the PEPFAR program for the following products:

- NDA 22-294 Zidovudine 60mg Tablets
- NDA 22-296 Lamivudine/Zidovudine 30 mg/60 mg Tablets

The following comments are being conveyed on behalf of the Review Team, and are directed towards your June 2, 2008 submission. During our upcoming teleconference meeting with you on July 21, 2008, we will be prepared to clarify any questions you have regarding these comments. Reference in made to our June 27, 2008 information request in response to your June 2, 2008 submission, which included responses to our original comments sent to you on May 8, 2008, via email correspondence regarding your March 17, 2008 submission. Please respond via email correspondence and send an archival copy of your responses to your NDAs.

For NDA 22-294 and 22-296

We appreciate your June 2, 2008 submission providing additional literature references for dosing justification for zidovudine twice daily administration and zidovudine/lamivudine fixed dose tablet. However, the submitted information is not sufficient to file these applications. For the zidovudine NDA, corresponding projected zidovudine exposures to support twice daily dosing

according to weight bands is needed. In addition, if the projected exposures differ from the approved recommended daily dose, efficacy and safety data to support these differences are needed. Similar data are needed to support the zidovudine/lamivudine fixed dose tablet. Projected exposures for both zidovudine and lamivudine at the proposed weight bands and supporting efficacy and safety data are needed. We have provided a hypothetical example to illustrate the type of information and rationale needed to support your proposed NDA submissions. The supporting efficacy and safety data can come from the Retrovir, Epivir or Combivir labels approved in the United States, literature or other sources. We look forward to working with you on the necessary information to support your NDA submissions and we can provide additional clarification during July 21, 2008, teleconference meeting.

Example:

The proposed Drug X pediatric dosing is as follows:

Weight (kg)	**Dosage Using 50 mg Tablet**		**Total Daily Dose**
	AM Dose	PM dose	
10 to 20	½ tablet (25 mg)	½ tablet (25 mg)	50 mg
>20 to <30	½ tablet (25 mg)	1 tablet (50 mg)	75 mg
≥30	1 tablet (50 mg)	1 tablet (50 mg)	100 mg

Summary of Pharmacokinetic Data

When actual pharmacokinetic data are not available for the scored tablet for use in children, results from pharmacokinetic modeling and simulation are needed along with historical pediatric pharmacokinetic data from approved dosing regimens for comparison. Additionally, you can use historical adult pharmacokinetic data to further support your proposed dosing recommendations.

Weight (kg)	Projected AUC	AUC Historical Pediatric Data	% difference
10	13	11	+18%
20	15	17	-12%
21	23	19	+21%
29	24	26	-8%
30	30	26	+15%
Weight (kg)	Projected Cmax	Cmax Historical Pediatric Data	% difference
10	1.12	1.5	+34%
20	1.7	1.5	+13%
21	2	2.1	-5%
29	2.4	2.7	-15%
30	2.4	3.0	+25%

Given the potential changes in Drug X exposures across the weight groups, the available safety and efficacy data to support these changes are needed and can be summarized as follows.

Efficacy evaluation

Provide rationale why a 12% decrease in AUC exposures (greatest AUC decrease across weight bands) is not expected to adversely affect efficacy.

Safety evaluation

Provide rationale with supporting documentation from literature describing any impact on safety profile for a 34% increase in Cmax exposures. Literature data evaluating Drug X at higher doses could provide supportive information. Please include both incidence of adverse event and laboratory abnormality data to support your position.

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

Sincerely yours,

Monica Zeballos, Pharm.D.
USPHS, LCDR
Senior Program Consultant
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug and Evaluation Research

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/s/

Monica Zeballos
7/17/2008 08:25:53 PM
CSO

Monica Zeballos
7/17/2008 08:26:32 PM
CSO

MEMORANDUM

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

DATE: June 27, 2008

TO: Blessy Johns, U.S. Agent for Aurobindo Pharma Limited

FROM: Monica Zeballos, Pharm.D., Sr. Program Consultant, Division of Antiviral Products (DAVP)

CONCUR: Kim Struble, Pharm.D., Medical Team Leader, DAVP
Regina Alivisatos, M.D. Medical Reviewer, DAVP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Shirley Lu, Ph.D., Clinical Pharmacology Reviewer, DCP4, OCP, OTS
Stephen Miller, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment 2 (DPA2), Office of New Drug Quality Assessment (ONDQA)
Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA
Ted Chang, Ph.D., Chemistry Reviewer, DPA2, ONDQA
George Lunn, Ph.D., Chemistry Reviewer, DPA2, ONDQA

NDAs: 22-294 and 22-296

APPLICANT: Aurobindo Pharma Limited

DRUGS: Zidovudine 60mg and Lamivudine/Zidovudine 30 mg/60 mg

SUBJECT: Information Request

Please refer to your New Drug Applications (NDAs) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for procurement under the PEPFAR program for the following products:

- NDA 22-294 Zidovudine 60mg Tablets
- NDA 22-296 Lamivudine/Zidovudine 30 mg/60 mg Tablets

The following responses are being conveyed on behalf of the Review Team, and are directed towards your June 2, 2008 submission, which included responses to our original comments sent to you on May 8, 2008, via email correspondence regarding your March 17, 2008 submission.

Please respond via email correspondence and send an archival copy of your responses to your NDAs.

For convenience of review, all our May 8, 2008 comments in bold, your responses in italics, and today's responses in bold and underlined have been reproduced.

For NDA 22-294 and 22-296

FDA Comment No. 1: We received and reviewed your submission dated March 17, 2008, providing additional literature references and dosing justification for zidovudine. This information is not sufficient to file these applications. Please submit corresponding projected zidovudine exposures to support dosing according to weight bands. We encourage you to collaborate with other investigators and review the WHO reports entitled: "Preferred antiretroviral medicines for treating and preventing HIV infection in younger children" (link: http://www.who.int/hiv/events/paediatricmeetingreport.pdf) and "Paediatric Antiretroviral Drugs: Dosing."

Aurobindo Response to No. 1: As per your suggestion, we have now referred to WHO's report[1] entitled "Preferred antiretroviral medicines for treating and preventing HIV infection in ....see official submission for the rest of the answer.

FDA Response dated June 27, 2008: The additional literature references and twice a day dosing justification for zidovudine are not sufficient to file these applications at this time because our original request to submit corresponding projected zidovudine exposures to support twice a day dosing according to weight bands is still outstanding.

FDA Comment No. 2: Additionally, please submit the following information:

- **Justification for the solid oral dosing in children in the lower weight bands, specifically the 3-5.9 kg weight band which may include infants too young to take a solid or crushed formulation**

Aurobindo Response to No. 2: Zidovudine Tablets USP 60 mg and Lamivudine 30 mg and Zidovudine 60 mg tablets can be crushed and given to children above 6 months of age weighing between 3-5.9 kg as explained in response to the first question.

- **Supporting documentation if either tablets are dispersible in water or other medium**

Aurobindo Response to No. 2: Zidovudine Tablets USP 60 mg and Lamivudine 30 mg and Zidovudine 60 mg tablets are not dispersible in nature.

FDA Response dated June 27, 2008: On your June 9, 2008 email correspondence, you provided the following clarification with regard to crushing a tablet without being able to disperse it in any type of liquid or other medium:

- *Please note that the tablets are conventional tablets with a breakline. We have been told that in resource limited settings, such tablets are crushed using mortar and pestle at the home of the patient and the powder is administered in food or drink to children. We are aware that such a practice will never be adopted in USA but the products are not meant for marketing in the US market. They are meant for marketing in PEPFAR countries only where use of crushed tablets is common.*

Please note that any labeling (i.e., PI, PPI, immediate container, carton, and blister pack labels) statement regarding dosing younger children not able to swallow tablets must to be supported by stability data. If this type of approach is important, you will need to submit draft labeling statements specifying the liquid in which the tablet is to be dispersed, along with suitable short-term data to show the stability of the actives in that liquid.

For NDA 22-294

FDA Comment No. 1: Because of the lapsed exclusivity in the United States for Retrovir® (zidovudine) 300 mg tablets, NDA 22-294 is eligible for a full approval and not a tentative approval action. Therefore, please confirm that you will comply with the following requirements associated with a full approval action:

- **Implementation of the Physician's Labeling Rule (PLR) [21 CRF 201.56, 201.57]. For additional information, please refer to the Draft FDA Guidance for Industry on: *Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements* (January 2006) or refer to the FDA website link: http://www.fda.gov/cder/regulatory/physLabel/. We acknowledge that you complied with the implementation of the Structured Product Labeling (SPL) requirement.**

  Aurobindo Response to No. 1: We hereby commit that we will implement Physician's labeling Rule in accordance with 21 CFR 201.56 and 201.57. We will comply the requirements of physician labeling rule in our proposed package insert once it gets implemented for innovator package insert i.e., Retrovir Tablets

  FDA Response dated June 27, 2008: On your June 9, 2008 email correspondence, you stated that you are ready to implement the PLR requirement for the package insert. We appreciate your efforts but until the requested literature and dosing justification data for zidovudine is found acceptable, we cannot file these applications even if the PLR requirement is met.

- **Implementation of the Food and Drug Administration Amendments Act (FDAAA), specifically the Pediatric Research Equity Act (PREA) requirement under Title IV and Postmarketing Drug Safety requirement under Title IX. For additional information for PREA, please refer to the Guidance for Industry on *How to Comply with the Pediatric Research Equity Act* or go the FDA website link: http://www.fda.gov/cder/pediatric. For additional information about FDAAA, please go to the FDA website link:**

http://www.fda.gov/oc/initiatives/advance/fdaaa.html. **A justification for the solid oral dosing in children in the lower weight bands is needed before we can determine if additional information is required under PREA.**

Aurobindo Response to No. 1: We have already provided the justification for the solid oral dosage in children in the lower weight bands in response to the first question and will wait for agency's information on the requirement for PREA based on the justification provided by us.

FDA Response dated June 27, 2008: As stated above, the additional literature references and twice a day dosing justification for zidovudine are not sufficient to file these applications at this time because our original request to submit corresponding projected zidovudine exposures to support twice a day dosing according to weight bands is still outstanding. Additionally, our originally request to provide justification for the solid oral dosing in children in the lower weight bands before we can determine if additional information is required under PREA is also outstanding.

- **Fully approved products should comply with all applicable U.S. regulations. Please provide an overview of how the zidovudine drug product complies with: a) 21 CFR 206 regarding uniqueness of dosage form appearance and with, b) the expectations regarding child-resistant packaging in 16 CFR 1700.**

Aurobindo Response to No. 1: a) We hereby providing the imprint dosage form of our drug product in accordance with 21 CFR 206. The imprint dosage form of the drug product photo color print PDF is also enclosed as (Attachment -4) for your reference.

FDA Response dated June 27, 2008: We are currently reviewing the submitted information regarding the uniqueness of dosage form appearance and will let you know if additional information is needed.

b) Our container pack of 60's count is Child Resistant Pack and our container pack of 1000's count is specifically for the pharmacies which in turn will dispensed them in CRC bottle. Our Blister packs are non CRC and as confirmed by us to agency in our previous communication that Zidovudine Tablets USP 60 mg is not intended to market in USA. The blister pack is designed only for PEPFAR market.

FDA Response dated June 27, 2008: Please submit in writing a commitment that you will ensure that all the packaging will conform with the consumer safety regulations per 16 CFR 1700 prior to marketing your product in the United States.

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

Sincerely yours,

Monica Zeballos, Pharm.D.
USPHS, LCDR
Senior Program Consultant
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug and Evaluation Research

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/s/

Monica Zeballos
7/17/2008 08:21:39 PM
CSO

Monica Zeballos
7/17/2008 08:22:27 PM
CSO

MEMORANDUM

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

DATE:	May 8, 2008
TO:	Blessy Johns, U.S. Agent for Aurobindo Pharma Limited
FROM:	Monica Zeballos, Pharm.D., Sr. Program Consultant, Division of Antiviral Products (DAVP)
CONCUR:	Jeffrey Murray, M.D., M.P.H., Deputy Director, DAVP Kim Struble, Pharm.D., Medical Team Leader, DAVP Linda Lewis, M.D. Medical Team Leader, DAVP Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS) Stephen Miller, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment 2 (DPA2), Office of New Drug Quality Assessment (ONDQA) Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA
NDAs:	22-294 and 22-296
APPLICANT:	Aurobindo Pharma Limited
DRUGS:	Zidovudine 60mg and Lamivudine/Zidovudine 30 mg/60 mg
SUBJECT:	Information Request

Please refer to your New Drug Applications (NDAs) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for procurement under the PEPFAR program for the following products:

- NDA 22-294 Zidovudine 60mg Tablets
- NDA 22-296 Lamivudine/Zidovudine 30 mg/60 mg Tablets

The following information request is being conveyed on behalf of our Review Team. Please respond via email correspondence and send an archival copy of your responses to your NDAs.

For NDA 22-294 and 22-296

1. We received and reviewed your submission dated March 17, 2008, providing literature references and dosing justification for zidovudine. This information is not sufficient to file these applications. Please submit corresponding projected zidovudine exposures to support dosing according to weight bands. We encourage you to collaborate with other investigators and review the WHO reports entitled: "Preferred antiretroviral medicines for treating and preventing HIV infection in younger children" (link: http://www.who.int/hiv/events/paediatricmeetingreport.pdf) and "Paediatric Antiretroviral Drugs: Dosing."

2. Additionally, please submit the following information:

   - Justification for the solid oral dosing in children in the lower weight bands, specifically the 3-5.9 kg weight band which may include infants too young to take a solid or crushed formulation
   - Supporting documentation if either tablets are dispersible in water or other medium

For NDA 22-294

1. Because of the lapsed exclusivity in the United States for Retrovir® (zidovudine) 300 mg tablets, NDA 22-294 is eligible for a full **approval** and not a **tentative approval** action. Therefore, please confirm that you will comply with the following requirements associated with a full approval action:

   - Implementation of the Physician's Labeling Rule (PLR) [21 CRF 201.56, 201.57]. For additional information, please refer to the Draft FDA Guidance for Industry on: *Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements* (January 2006) or refer to the FDA website link: http://www.fda.gov/cder/regulatory/physLabel/. We acknowledge that you complied with the implementation of the Structured Product Labeling (SPL) requirement.

   - Implementation of the Food and Drug Administration Amendments Act (FDAAA), specifically the Pediatric Research Equity Act (PREA) requirement under Title IV and Postmarketing Drug Safety requirement under Title IX. For additional information for PREA, please refer to the Guidance for Industry on *How to Comply with the Pediatric Research Equity Act* or go the FDA website link: http://www.fda.gov/cder/pediatric. For additional information about FDAAA, please go to the FDA website link: http://www.fda.gov/oc/initiatives/advance/fdaaa.html. A justification for the solid oral dosing in children in the lower weight bands is needed before we can determine if additional information is required under PREA.

   - Fully approved products should comply with all applicable U.S. regulations. Please provide an overview of how the zidovudine drug product complies with: a) 21 CFR 206 regarding uniqueness of dosage form appearance and with, b) the expectations regarding child-resistant packaging in 16 CFR 1700.

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

Sincerely yours,

Monica Zeballos, Pharm.D.
USPHS, LCDR
Senior Program Consultant
Division of Antiviral Products
Office of Antimicrobial Products

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
5/8/2008 02:50:56 PM
CSO

Monica Zeballos
5/8/2008 02:51:31 PM
CSO

December 13, 2007

Food and Drug Administration
Rockville MD 20857

Prasada Kambham
U.S. Agent for Aurobindo Pharma Limited
Aurobindo Pharma USA Inc.
2400 Route 130 North
Dayton, NJ 08810

RE: NDA 22-294, Pediatric Zidovudine Tablets, 60 mg, Fiscal Year 2008 Application Fee Waiver Request 2008.019

Dear Mr. Kambham:

This responds to your November 2, 2007, and December 1, 2007, letters requesting a waiver of user fees under the barrier-to-innovation waiver provision, section 736(d)(1)(B)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (waiver request 2008.019). You request a waiver of the fiscal year (FY) 2008[2] application fee for new drug application (NDA) 22-294 for pediatric zidovudine tablets, 60 milligrams (mg), and a waiver of the establishment fees.[3] For the reasons described below, the Food and Drug Administration (FDA) grants the request of Aurobindo Pharma Limited (Aurobindo) for a barrier-to-innovation waiver of the FY 2008 application fee for NDA 22-294, pediatric zidovudine tablets, 60 mg.

I. Aurobindo's Request

According to your request for a waiver of the application fee, Aurobindo is actively participating in the President's Emergency Plan for AIDS Relief (PEPFAR) program by submitting applications for a wide range of antiretroviral drug products. You state that to date you have received tentative/final approval for 16 abbreviated new drug applications and 3 NDAs. You further state that you are now adding solid oral dosage forms to the pediatric dosage range in line with recommendations in an attached World Health Organization (WHO) draft expert report. In addition, you state the following:

- Upon receipt of a tentative approval of your NDA, zidovudine tablets would be made available for procurement under the PEPFAR program at competitive prices.

[1] 21 U.S.C. 379h(d)(1)(B).
[2] Fiscal year 2008 = October 1, 2007, through September 30, 2008.
[3] You requested a waiver of the application fee and the annual establishment fee based on the barrier-to-innovation criteria. This response is valid only for the application fee for NDA 22-294. Aurobindo has not been assessed establishment fees, nor is it the Food and Drug Administration's (FDA's) plan to assess establishment fees until your application is approved. The Agency does not assess establishment fees for products that are not approved. Therefore, it is not necessary for FDA to act on your request for a waiver of establishment fees. If Aurobindo is assessed establishment fees, you may submit a new waiver request no later than 180 days after payment of the establishment fee is due.

track status.[6] We will also consider the existence of treatment alternatives. The existence of treatment alternatives will weigh against deciding that a product is innovative.

III. Evaluation of Aurobindo'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 Aurobindo's product, pediatric zidovudine tablets, innovative?

In the HIV guidance,[7] FDA encouraged sponsors to submit certain applications for fixed dose combination and co-packaged HIV products. In addition, the HIV guidance document stated that the principles outlined in the guidance also apply to single-ingredient copies of antiretroviral drugs that are components of the regimens listed in Appendix B. We have confirmed that your single ingredient product is a component on the list of examples in Attachment B of the HIV guidance. Because the active ingredient has been previously approved, your product will not be considered a new molecular entity. The application has not been identified for a priority review but will be given a fast track designation. FDA also considers that the products listed in Attachment B to the HIV guidance[8] are innovative, because such simplified regimens that will facilitate distribution and patient compliance, particularly in treatment-naïve patients, are needed in developing countries.[9] In addition, FDA recognizes that pediatric patients need to have access to drugs that can benefit them. FDA also recognizes that new single drug pediatric products in small tablet formulations may be logistically easier to store, ship, and administer than currently approved formulations, which are typically solutions or powders for solutions. New single drug tablet pediatric formulations may have longer shelf lives, and may circumvent the need for refrigeration and a pharmacist or learned intermediary to reconstitute the formulation. Single dose pediatric formulations may lay the groundwork for further development of pediatric fixed dose combinations. We believe that new pediatric tablet formulations could fulfill important pediatric health care needs of developing and PEPFAR nations. Considering all the factors noted above, FDA finds that Aurobindo's pediatric zidovudine tablets is a product that, for user fee waiver purposes, is innovative.[10]

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

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[6] 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/cder/guidance.

[7] FDA's October 2006 guidance for industry, *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV*.

[8] Attachment B includes zidovudine in several regimens.

[9] Please refer to FDA's February 2007 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/cder/guidance, for a full discussion of why FDA currently considers fixed dose combinations or co-packaged products for the treatment for HIV to be innovative.

[10] Please note that after sufficient 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.

- You provided evidence that the product is listed on an HIV treatment guideline for one or more PEPFAR countries.

- The submission of an application for approval of pediatric zidovudine tablets has been planned and scheduled in many of the PEPFAR countries.

Consequently, considering all the relevant factors, your request for a barrier-to-innovation waiver of the FY 2008 application fee for NDA 22-294 for pediatric zidovudine tablets, 60 mg, is granted. We have notified the Office of Financial Management of this waiver decision and have asked them to waive the application fee for Aurobindo's NDA 22-294, pediatric zidovudine tablets, 60 mg, provided that FDA receives the marketing application for the NDA no later than 1 year from the date of this letter.

If FDA refuses to file the application or Aurobindo withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should Aurobindo resubmit its marketing application. If this situation occurs, Aurobindo should contact this office approximately 45 days before the company expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

V. Disclosure of Public Information

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. 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

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

product in the United States, the FDA finding that you have satisfied the criteria for a PEPFAR waiver may change in the evaluation of future waiver requests.

AUROBINDO

Dated 01st December 2007

To,

Ms. Jane Axelrad
Associate Director of Regulatory Policy
FDA/CDER/office of Regulatory Policy
Center for Drug Evaluation and Research
Food and Drug Administration
5515 Security Lane, HFD-005
Rockville, MD 20852

Dear Ms. Jane,

Subject: Commitment for not marketing Pediatric Zidovudine Tablets USP 60 mg (NDA#22-294) in US market

This has reference to the telecon we had with the Agency's representatives, Mr. David Araojo and Mr. Jeff on 30th November 2007 whereby they have advised that if we needed user fee waiver for the proposed 505 (b)(2) application of Pediatric Zidovudine Tablets USP 60 mg, we would need to commit that we will not market the said product in US Market. Aurobindo Pharma Limited hereby commits not to market Pediatric Zidovudine Tablets USP 60 mg in US market after getting tentative approval from the Agency. The subject product is intended to be marketed under PEPFAR initiative in one or more of the 15 designated PEPFAR countries.

If you require any further clarification, please contact the undersigned at Aurobindo Pharma Limited, 313, Bachupally, Quthubullapur Mandal, Hyderabad, India – 500072.

Thanking You,

For Aurobindo Pharma Limited

Rao

Dr.Gita Rao
Principal Scientist – Regulatory Affairs
Email: gitarao@aurobindo.com