

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22-294**

**OTHER REVIEW(S)**

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

<b>Application Information</b>		
NDA # <b>22-294</b> BLA#	NDA Supplement #:S- NA BLA STN #	Efficacy Supplement Type SE- NA
Proprietary Name: <b>NA because product will not be marketed in the U.S. per Applicant's commitment in writing &amp; was submitted under PEPFAR</b> Established/Proper Name: <b>Zidovudine</b> Dosage Form: <b>Tablets (scored)</b> Strengths: <b>60 mg</b>		
Applicant: <b>Aurobindo Pharma Limited</b> Agent for Applicant (if applicable): <b>Blessy Johns</b>		
Date of Application: <b>03Oct08</b> Date of Receipt: <b>07Oct08</b> Date clock started after UN:		
PDUFA Goal Date: <b>17August09</b>		Action Goal Date (if different): <b>23July09</b>
Filing Date: <b>6Dec08</b> Date of Filing Meeting: <b>02Dec08</b>		
Chemical Classification: (1,2,3 etc.) (original NDAs only) <b>3 (new dosage form)</b>		
Proposed Indication(s): <b>HIV-1 treatment</b>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product): NA	
List referenced IND Number(s): NA	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
User Fee Status  Comments: waived under the barrier-to-innovation	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  # years requested:  <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>

<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>	
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4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? *Check the Electronic Orange Book at: <http://www.fda.gov/cder/ob/default.htm>*

YES  
 NO

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

*If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.*

**Note:** In July 2009, Beth Duvall-Miller, OND, RA Team Leader, and Kim Quaintance, OND IO ADRA, determined for all NDAs classified as 505(b)(2)s submitted under PEPFAR, regardless of the action granted (TA, A, CR), the 505(b)(2) assessment form (replaces Appendix B of NDA regulatory filing review) does not have to be completed or submitted for clearance. Therefore, there is no 505(b)(2) assessment form for this application.

**Format and Content**

*Do not check mixed submission if the only electronic component is the content of labeling (COL).*

**Comments:**

All paper (except for COL)  
 All electronic  
 Mixed (paper/electronic)

CTD  
 Non-CTD  
 Mixed (CTD/non-CTD)

**If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?**

**Module 2, formulation data, in vitro data**

**If electronic submission:**  
paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?

*Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

**Comments:**

YES  
 NO

**If electronic submission, does it follow the eCTD guidance?**  
(<http://www.fda.gov/cder/guidance/7087rev.pdf>)

YES  
 NO

**If not, explain (e.g., waiver granted):**

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p> <p><b>There is no space on the form for both signatures. This was cleared by ADRA Dave Roeder.</b></p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain: Debarment certification was not signed by applicant &amp; agent.</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>Patent Information (NDAs/NDA efficacy supplements only)</b></p>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments: 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.</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>

<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p><b>Comments: Requested to revise it to include agent and applicant's signature</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/> Not Applicable ( <i>electronic submission or no CMC technical section</i> ) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments: Not applicable for clinical studies because this is a 505b2 NDA that relies on the Agency's previous findings of safety and efficacy for the listed drug (i.e., clinical data in approved PI) &amp; applicant does not own/have right of reference to the data supporting the approval.</b></p> <p><b>Not needed for BE studies because NDA will be evaluated based on a dissolution-supported biowaiver, linking the adult strength tablet formulation (ANDA 77-267 tentatively approved by OGD on 25August05) with this pediatric/lower strength tablet. Please see ONDQA Biopharmaceutics Review. Additionally, because the BE studies [fasted (Study No. Zid-01/04), fed (Study No. Zid-02/04)] conducted for the adult strength tablet formulation were already inspected under OGD's watch, we did not request DSI BE site inspections because there were no new clinical pharmacology sites involved.</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<b>Pediatrics</b>	
<p><b><u>PREA</u></b>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable See <b>Pediatric page for explanation that this application does not trigger PREA.</b></p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<b>Prescription Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not applicable</p> <p><input checked="" type="checkbox"/> Package Insert (PI)</p> <p><input type="checkbox"/> Patient Package Insert (PPI)</p> <p><input type="checkbox"/> Instructions for Use</p> <p><input type="checkbox"/> MedGuide</p> <p><input type="checkbox"/> Carton labels</p> <p><input checked="" type="checkbox"/> Immediate container labels</p> <p><input type="checkbox"/> Diluent</p> <p><input checked="" type="checkbox"/> Other (specify) <b>bulk packs labels (container)</b></p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p>	<p><input checked="" type="checkbox"/> YES</p>

<p><b>If no</b>, was a waiver or deferral requested before the application was received or in the submission?  <b>If before</b>, what is the status of the request?</p> <p style="text-align: center;"><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments: This NDA was submitted under PEPFAR and will not be marketed in the U.S.</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p><b>Comments: This NDA was submitted under PEPFAR and will not be marketed in the U.S.</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>REMS consulted to OSE/DRISK?</p> <p><b>Comments: Because 1) the listed drug (Retrovir Tabs, 300mg) did not trigger any requirements under Title IX (i.e., safety-related labeling changes, REMS), and 2) there are no new safety data available for this product, this NDA did not trigger Title IX either. Additionally, this application did not trigger PREA.</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p><b>Comments: This NDA was submitted under PEPFAR and will not be marketed in the U.S.</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 02Dec08

**NDA/BLA #:** 22-294

**PROPRIETARY/ESTABLISHED NAMES:** Zidovudine Tablets (scored), 60 mg

**APPLICANT:** Aurobindo Pharma Limited

**BACKGROUND:** This original NDA is a 505b2 application that relies on the Agency's previous findings of safety and efficacy for the listed drug & applicant does not own/have right of reference to the data supporting the approval. Additionally, this NDA was submitted under PEPFAR and provides for a scored tablet that dissolves or disperses in water for the pediatric population. 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. See letter attached at the end of this review.

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

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Monica Zeballos	Y
	CPMS/TL:		
Cross-Discipline Team Leader (CDTL)	Kellie Reynolds		Y
Clinical	Reviewer:	Regina Alivisatos	Y
	TL:	Kim Struble	Y
Social Scientist Review (for OTC products)	Reviewer:	NA	
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:	NA	

	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	NA	
	TL:		

Clinical Pharmacology	Reviewer:	Shirley Lu	Y
	TL:	Kellie Reynolds	Y
Biostatistics	Reviewer:	NA	
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	NA	
	TL:		
Statistics, carcinogenicity	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	George Lunn	Y
	PAL:	Stephen Miller	Y
	TL:	Norman Schmuff	N
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:	NA	
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:	NA	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	NA	
	TL:		
Other reviewers			

**OTHER ATTENDEES: Jeff Murray, Division Deputy Director**

505(b)(2) filing issues?  If yes, list issues:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments: Module 2, formulation data, in vitro data</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain: Not applicable for clinical studies because this is a 505b2 NDA that relies on the Agency's previous findings of safety and efficacy for the listed drug (i.e., clinical data in approved PI) &amp; applicant does not own/have right of reference to the data supporting the approval.</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><b>If no, for an original NME or BLA application, include the reason. For example:</b></p> <ul style="list-style-type: none"> <li>○ this drug/biologic is not the first in its class</li> <li>○ the clinical study design was acceptable</li> <li>○ the application did not raise significant safety or efficacy issues</li> <li>○ the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul> <p><b>Not needed for BE studies because NDA will be evaluated based on a dissolution-supported biowaiver, linking the adult formulation approved by OGD with this pediatric version (lower strength version). Please see ONDQA Biopharmaceutics Review.</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no, was a complete EA submitted?</b></p> <p><b>If EA submitted, consulted to EA officer (OPS)?</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES

<ul style="list-style-type: none"> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product?</li> </ul> <p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority: Monica Zeballos</b></p> <p><b>GRMP Timeline Milestones: They were established. See Review Timeline attached at the end of this review.</b></p> <p><b>Comments:</b></p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<input type="checkbox"/>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and</p>

	Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

**MEMORANDUM**

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

**DATE:** March 30, 2009

**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  
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

**NDA:** 22-294 and 22-296

**APPLICANT:** Aurobindo Pharma Limited

**DRUGS:** Zidovudine Tablets, 60mg and Lamivudine and Zidovudine  
Tablets, 30 mg/60 mg

**SUBJECT:** Labeling recommendations # 1

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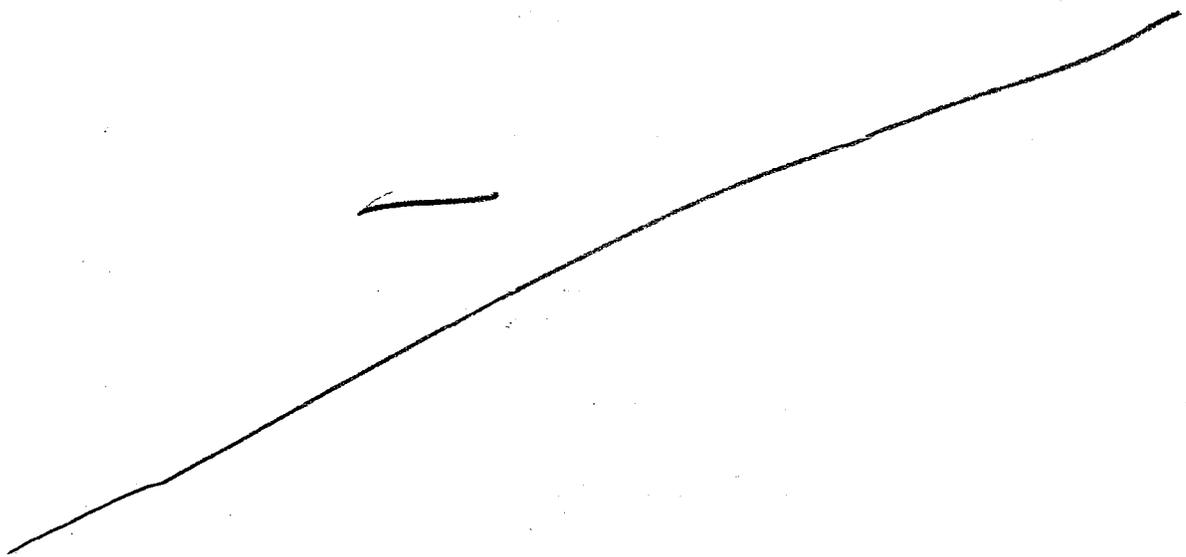
Please refer to your New Drug Applications (NDAs) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for procurement under the PEPFAR program for the following products:

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

The following labeling comments are being conveyed on behalf of our Review Team. Please revise the labeling for both applications by April 24, 2009, respond via email correspondence, and send an archival copy of your responses to your NDAs. These updated versions of the labeling will be used for further revisions.

For NDA 22-294

1. Please see the Division's labeling recommendations for the twice daily dosing regimen in children weighing 4 kg or greater. Please incorporate these changes into the DOSAGE AND ADMINISTRATION section of the labeling.



b(4)

**Recommended Pediatric Dosage of Zidovudine Tablets**

Weight (kg)	Dosage Regimen Using Scored 60 mg Tablets		Total Daily Dose
	AM Dose	PM Dose	
4 to 6	1 tablet (60 mg)	1 tablet (60 mg)	120 mg
6.1 to 11	1.5 tablet (90 mg)	1.5 tablet (90 mg)	180 mg
11.1 to 14	2 tablets (120 mg)	2 tablets (120 mg)	240 mg
14.1 to 18	2.5 tablets (150 mg)	2 tablets (150 mg)	300 mg
18.1 to 22	3 tablets (180 mg)	3 tablets (180 mg)	360 mg
22.1 to 25	3.5 tablets (210 mg)	3.5 tablets (210 mg)	420 mg
25.1 to 28	4 tablets (240 mg)	4 tablets (240 mg)	480 mg
28.1 to < 30	5 tablets (300 mg)	5 tablets (300 mg)	600 mg

Safety and efficacy have not been established in patients weighing less than 4 kg

2. To comply with the implementation of the PREA requirement under FDAAA, please revise the pediatric waiver request to include pediatric patients from birth to less than 6 weeks of age or less than 4 kg. Please note that you do not need to submit a pediatric deferral request for this application.

**For NDA 22-296**

1. Please be advised that the Division has proposed an alternative dosing regimen. The Division's proposal has the benefits of exact correlation for the zidovudine component (beginning from the 5 kg weight), dosing up to 30 kg, and fewer instances of lower lamivudine exposures as compared to the originally proposed regimen.

We have the following recommendations for the DOSAGE AND ADMINISTRATION section:

The recommended oral dose of Lamivudine and Zidovudine Tablets (30 mg/60 mg) twice daily for adolescents and pediatric patients is based on body weight. The following table lists the dosage schedule of Lamivudine and Zidovudine Tablets, 30mg/60mg twice daily for patients with body weight less than 30 kg.

**Recommended Pediatric Dosage of Lamivudine and Zidovudine Tablets**

Weight (kg)	Dosage Regimen Using Scored Lamivudine and Zidovudine 30 mg/60 mg Tablets*		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5 - 6	1 tablet (30 mg L/60 mg Z)	1 tablet (30 mg L/60 mg Z)	60L/120Z
6.1 - 11	1.5 tablet (45 mg L/90 mg Z)	1.5 tablet (45 mg L/90 mg Z)	90L/180Z
11.1 - 14	2 tablets (60 mg L/120 mg Z)	2 tablets (60 mg L/120 mg Z)	120L/240Z
14.1 - 18	2.5 tablets (75 mg L/150 mg Z)	2.5 tablets (75 mg L/150 mg Z)	150L/300Z
18.1 - 22	3 tablets (90 mg L/180 mg Z)	3 tablets (90 mg L/180 mg Z)	180L/360Z
22.1 - 25	3.5 tablets (105 mg L/210 mg Z)	3.5 tablets (105 mg L/210 mg Z)	210L/420Z
25.1 - 28	4 tablets (120 mg L/240 mg Z)	4 tablets (120 mg L/240 mg Z)	240L/480Z
28.1 - < 30	4.5 tablets (135 mg L/270 mg Z)	4.5 tablets (135 mg L/270 mg Z)	270L/540Z

\*L= lamivudine; Z= zidovudine

For children weighing greater than or equal to 30 kg, the recommended dose is the adult maximum daily dose of lamivudine 150 mg twice daily and zidovudine 300 mg twice daily.

If you have any questions, please contact me at (301) 796-0840 or via email at [monica.zeballos@fda.hhs.gov](mailto: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 Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Monica Zeballos  
3/30/2009 03:52:03 PM  
CSO

Monica Zeballos  
3/30/2009 03:53:02 PM  
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