CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-294

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-294
TYPE: 505 (b)(2); PEPFAR
DRUG: Zidovudine, 60 mg Tablets
SPONSOR: Aurobindo Pharma Limited

REVIEWER: Shirley K. Lu, Ph.D.
TEAM LEADER: Kellie S. Reynolds, Pharm.D.
SUBMISSION DATE(S): October 7, 2008

Executive Summary

Aurobindo submitted two 505 (b)(2) applications under the President's Emergency Plan for AIDS Relief (PEPFAR) program for Zidovudine (ZDV) 60 mg and Lamivudine/Zidovudine (LMV/ZDV) 30/60 mg scored tablets. This review addresses the information submitted in support of a full approval for ZDV, 60 mg tablets. This product is eligible for full approval since the patent for Retrovir (the reference brand product) has expired.

Aurobindo has full approval of the same product at a higher strength (300 mg) under ANDA 77-267. A biowaiver for the proposed lower strength tablet has been granted by ONDQA biopharmaceutics group on the basis of formulation proportionality and acceptable dissolution data. The formulations of the higher and lower strength tablets are proportionally identical. Thus, the decision regarding approval of this application is based on the similarity between the proposed and approved doses and the available efficacy and safety information included in Retrovir's label.

Recommendations

The Office of Clinical Pharmacology (OCP) reviewed the information submitted and concluded that the established safety and efficacy data for ZDV support twice daily dosing in children weighing between 4 kg and 30 kg using a modified version of the sponsor's proposed doses. b(4)

The division-recommended dosing table is as follows:

ZDV Tablets, 60 mg

Weight of Child (kg)	# of tablets 2X Daily	Amount per dose (mg)	Total daily dose (TDD) (mg)
4 to 6	1	60	120
6.1 to 11	1.5	90	180
11.1 to 14	2	120	240
14.1 to18	2.5	150	300
18.1 to 22	3	180	360
22.1 to 25	3.5	210	420
25.1 to 28	4	240	480
28.1 to <30	4.5	270	540
≥30	5	300	600

Clinical Pharmacology Findings for NDA 22-294

No new studies were conducted in support of this application. The basis of approval of NDA 22-294 are from the following sources of information:

- A comparison of the proposed doses with the approved doses in the Retrovir label
- Knowledge of the exposures resulting from the proposed doses (from the Retrovir label and literature)

- Safety and efficacy data from available literature publications that support the potential deviations from the approved doses

Aurobindo proposed —— BID —— dosing regimen for their scored tablet. The following is the U.S. approved pediatric dosing regimen for Retrovir: b(4)

➢ ZDV (Retrovir):

Weight	Total Daily Dose	Regimen	
		BID	TID
4 to <9 kg	24 mg/kg/day	12 mg/kg	8 mg/kg
9 to <30 kg	18 mg/kg/day	9 mg/kg	6 mg/kg
≥30 kg	600 mg/day	300 mg	200 mg

Alternatively, dosing for RETROVIR can be based on body surface area (BSA) for each child. The recommended oral dose of RETROVIR is 480 mg/m^2/day in divided doses (240 mg/m^2 twice daily or 160 mg/m^2 three times daily).

BID Regimen

Since the safety and efficacy of Retrovir's dosing regimen has already been established, the sponsor's proposed doses in each weight band were compared to approved doses of Retrovir. The basis of approval of the proposed twice daily regimen is the similarity in dose and exposure between Aurobindo's proposed dosing regimen and the approved BSA- and weight-based BID regimens for Retrovir. Since plasma ZDV concentrations increase proportionally with dose (between doses of 2 mg/kg q8h and 10 mg/kg q4h), there is a reasonable expectation that changes in dose will lead to proportionally similar changes in exposure. Thus, a comparison between the proposed doses and approved Retrovir doses was performed at each kg weight of a child using both the weight-based and BSA-based doses as a reference. The sponsor's proposed BID dosing regimen for the ZDV tablet, 60 mg (NDA 22-294) are shown below.

Table 1

Aurobindo's proposed dosing for ZDV BID regimen:

Weight of Child (kg)	# of tablets 2X Daily	Amount per dose (mg)	Total daily dose (TDD) (mg)
4 to 6	1	60	120
6.1 to 11	1.5	90	180
11.1 to 14	2	120	240
14.1 to18	2.5	150	300
18.1 to 22	3	180	360
22.1 to 25	3.5	210	420
25.1 to 28	4	240	480

The above table does not include dosing recommendations for children weighing between 28 and 30 kg. The pediatric dosing regimen for Retrovir includes dosing recommendations for children up to 30 kg. Thus, the DAVP-modified dosing table is shown below (changes in bold):

Table 2
Modified dosing table for ZDV BID regimen:

Weight of Child (kg)	# of tablets 2X Daily	Amount per dose (mg)	Total daily dose (TDD) (mg)
4 to 6	1	60	120
6.1 to 11	1.5	90	180
11.1 to 14	2	120	240
14.1 to18	2.5	150	300
18.1 to 22	3	180	360
22.1 to 25	3.5	210	420
25.1 to 28	4	240	480
28.1 to <30	**4.5**	**270**	**540**
30	**5**	**300**	**600**

Table 3
Differences between modified Aurobindo dose and Retrovir's two approved dosing regimens

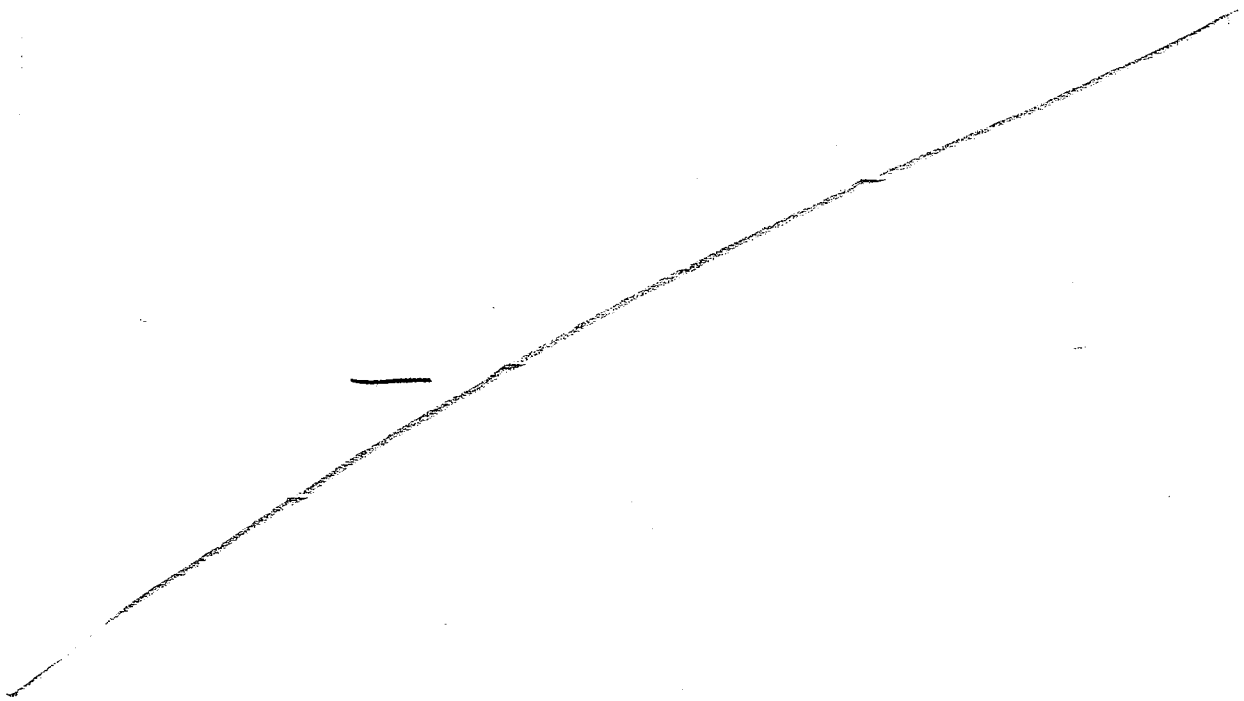
	Aurobindo	**Retrovir weight-based dose**	**% Diff. wt-based**	**Retrovir BSA-based dose**	**% Diff. BSA-based**
Weight in kg	BID (mg, per dose)	BID (mg, per dose)		(based on 50th percentile for ht. and wt.)	
4	60	48	**25.0**	54	10.1
5	60	60	0.0	64	-6.4
6	60	72	-16.7	73	-17.5
6.1	90	73	**23.0**	73	**23.8**
7	90	84	7.1	80	11.9
8	90	96	-6.3	88	2.2
9	90	81	11.1	96	-6.7
10	90	90	0.0	104	-13.4
11	90	99	-9.1	113	**-20.3**
11.1	120	100	**20.1**	113	6.2
12	120	108	11.1	123	-2.1
13	120	117	2.6	133	-9.7
14	120	126	-4.8	142	-15.2
14.1	150	127	18.2	142	6.0
15	150	135	11.1	151	-0.9
16	150	144	4.2	160	-6.3
17	150	153	-2.0	168	-10.6
18	150	162	-7.4	176	-14.8
18.1	180	163	10.5	177	2.2
19	180	171	5.3	183	-1.7
20	180	180	0.0	191	-5.7
21	180	189	-4.8	197	-8.8
22	180	198	-9.1	205	-12.2
22.1	210	199	5.6	205	2.4

23	210	207	1.4	213	-1.3
24	210	216	-2.8	219	-4.2
25	210	225	-6.7	227	-7.5
25.1	240	226	6.2	227	5.6
26	240	234	2.6	233	3.1
27	240	243	-1.2	240	0.1
28	240	252	-4.8	246	-2.5
28.1	270	253	6.7	246	9.6
29	270	261	-8.0	253	6.9
30	300	300	0.0	258	16.4

-Differences in dose >20% are in **bold**.
-Doses shaded in gray are changes added by the Division.

When comparing Aurobindo's proposed tablet dosing (Table 2) with Retrovir syrup dosing, differences in dose would be expected due to Aurobindo's weight band dosing to accommodate a tablet with a fixed dose. For instance, children weighing both 6.1 kg and 11 kg would receive the same tablet dose, while with Retrovir, they would receive different doses (73 mg vs. 99 mg, respectively). These differences cannot be avoided in most cases, however, the differences can be minimized based on the use of the half tablet and the number of cutoff points. The placement of the cutoff points does not to impact the differences in dose; it only shifts the location of the difference.

There are only two instances where the proposed dose varies by more than 20% from the BSA-based dose. These differences occur at the 6.1 kg breakpoint (+23%) and at the 11.1 kg breakpoint (-20.3%). Neither of these occurrences can be avoided when using the tablet formulation. Change of one or both cutoffs would lead to even greater differences in dose at other weights. In addition, from the Retrovir label, the weight-based dose for Retrovir differs by up to +19% and -22% as compared with the BSA-based dose for children at certain weights. Thus, the differences are within an acceptable range based on what has already been approved.



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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio Review Section- C

The existing safety and efficacy information available in Retrovir's label and published literature support twice daily dosing of ZDV 60-mg tablets in pediatric patients weighing between 4 kg and <30 kg. b(4)

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Concurrence:

Kellie S. Reynolds, Pharm.D.
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Shirley Lu
7/9/2009 03:29:52 PM
BIOPHARMACEUTICS

Kellie Reynolds
7/9/2009 03:46:42 PM
BIOPHARMACEUTICS

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-294
Submission Date:	12/18/07
Generic Name:	Zidovudine
Formulation:	Immediately release (IR) oral tablet
Strength:	60 mg (for pediatric use)
Sponsor:	Aurobindo
Type of submission:	Biowaiver request for this tablet strength 60 mg
Reviewer:	Tien-Mien Chen, Ph.D.

BACKGROUND

GSK's Retrovir (Zidovudine) IR 300 mg oral tablet (RLD; reference list drug) was approved by the Agency on 10/04/96. Retrovir in combination with other antiretroviral agents is indicated for the treatment of HIV infection. Retrovir capsules, syrup, and injectable dosage forms are also approved.

Aurobindo's generic zidovudine IR 300 mg oral tablet (ANDA 77-267) was approved on 09/19/05 by the Office of Generic Drug (OGD). To support the PEPFAR (US President's Emergency Plan for AIDS Relief) program, and based on WHO's rationale and the list of dosage recommendation, Aurobindo developed a smaller tablet strength (60 mg) intended for pediatric use in some developing countries, outside the US. Due to several environmental limitations, a syrup dosage form, though ideal, is not practical for storage conditions without refrigerators in these countries.

Upon agreement with the Agency, Aurobindo submitted NDA 22-294 under 505(b)(2) for the smaller zidovudine IR 60 mg oral tablets (scored). However, no bioequivalence (BE) study was conducted since currently there is no RLD of an IR 60 mg oral tablet. Under NDA 22-294, Aurobindo submitted 1) a biowaiver request for the IR 60 mg oral tablets since the proposed IR 60 mg oral tablet is exactly 1/5 of their currently approved generic IR 300 mg oral tablet and 2) comparative dissolution data between their 60 mg and 300 mg tablets. The above biowaiver request and the comparative dissolution data are therefore reviewed here.

FORMULAITON COMPARISONS

The formulation and composition of zidovudine IR 300 and 60 mg oral tablets are shown below.

b(4)

b(4)

The proposed IR 60 mg oral tablet is exactly 1/5 of their currently approved generic IR 300 mg oral tablet.

DISSOLUTION COMPARISONS

The dissolution methodology and results are shown below.

Dissolution Profile: Zidovudine Tablets USP 300 mg (Generic) and Zidovudine Tablets USP 60 mg (Pediatric)
Medium: Water (Currently approved), pH 1.2 buffer, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate buffer.
Volume: 900 mL
Temp.: 37°C ± 0.5°C
Apparatus: USP Apparatus II
Speed: 50 RPM
Time: 5, 10, 15, 20, 30, and 45 min

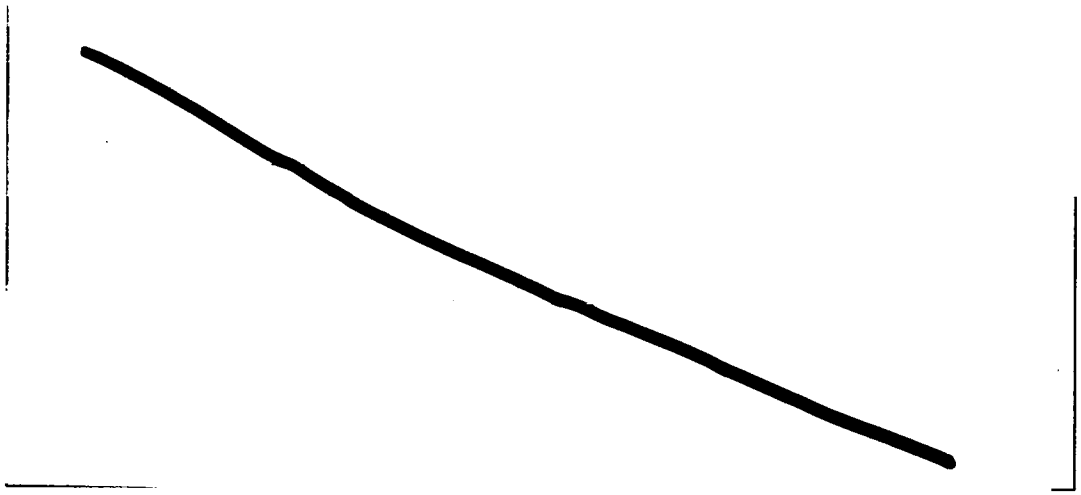
Table 2. Dissolution Results for 300 mg Tablet, Batch No. AA(121)002 and 60 mg Tablet, Batch No. RP(217)070 with f2 Calculation (for Water only)

Time (min)	Percentage of Drug Dissolved							
	Water		pH 1.2 Buffer		pH 4.5 Acetate Buffer		pH 6.8 Phosphate Buffer	
Strength	60 mg	300mg	60 mg	300 mg	60 mg	300 mg	60 mg	300 mg
5								
10								
15								
20								
30								
45								
f2 value:	—		----		------		-----	

b(4)

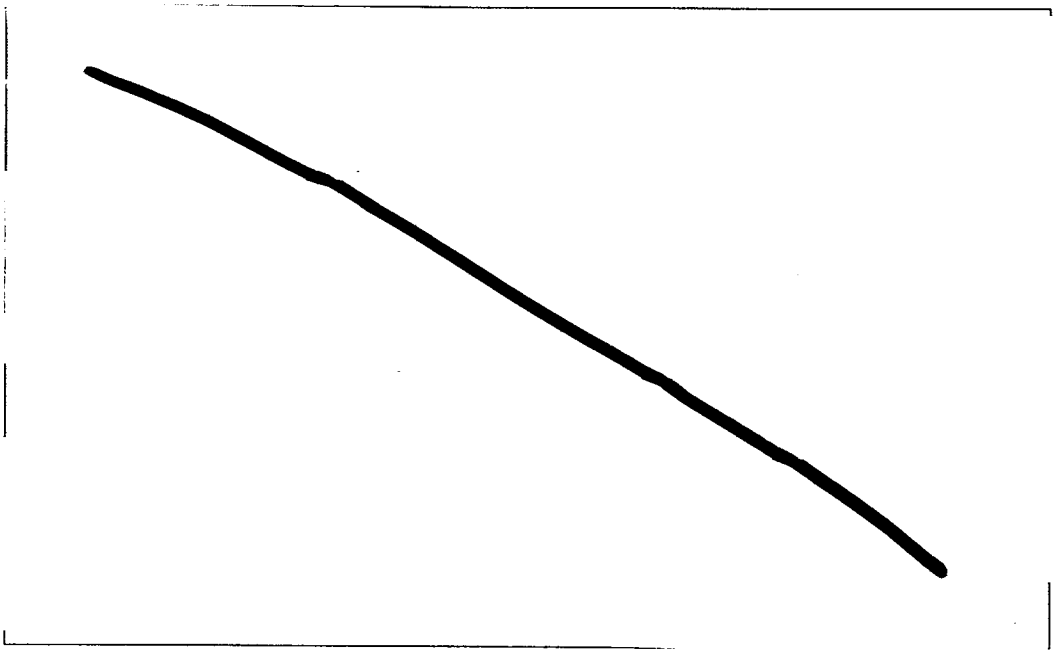
The comparative dissolution profiles in water and in all dissolution media are shown below.

Figure 1. **Comparative Dissolution Profiles of Zidovudine 300 and 60 mg Tablets in Water Medium**



b(4)

Figure 2. **Comparative Dissolution Profiles of Zidovudine 300 and 60 mg Tablets in Various Dissolution Media Tested**



b(4)

Additional comparative dissolution on three stability batches in water (n=12 tablets/batch) is shown below. All batches showed an acceptable f2 value, a range of [redacted] b(4)

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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Reviewer's Comments

Aurobindo's zidovudine IR 60 mg oral tablet indeed is exactly 1/5 of that of their currently approved generic IR 300 mg oral tablet. The f2 value is calculated (up to 15 min) for all 4 batches tested in water ranging from [redacted] indicating similarity in dissolution *in vitro* between 60 and 300 mg tablets. b(4)

The tablet is scored in order to provide smaller and/or appropriate doses for younger pediatrics. Although no additional dissolution data was provided for comparison between the whole (60 mg) and the half tablet (30 mg), the dissolution of the scored tablet is expected to be similar to the whole 60 mg tablet.

RECOMMENDATION

The biowaiver request that was submitted on 12/18/07 under NDA 22-294 for the proposed zidovudine IR 60 mg oral tablet plus comparative dissolution data with their currently approved generic IR 300 mg oral tablets are reviewed.

Form the Biopharmaceutics perspective, the biowaiver request for the proposed zidovudine IR 60 mg oral tablet could be granted. No further comments are to be conveyed to the sponsor.

05/15/09

Tien-Mien Chen, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

Date

CC: NDA
Patrick Marroum, Tien-Mien Chen

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/s/

Tien-Mien Chen
5/18/2009 10:58:39 AM
BIOPHARMACEUTICS
Minor revisions on second paragraph under Background section

Patrick Marroum
5/18/2009 11:01:40 AM
BIOPHARMACEUTICS