CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-294

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMORANDUM ADDENDUM

Date	July 20, 2009
From	Kimberly Struble, PharmD Medical Team Leader Review
NDA/BLA #	22-294
Applicant	Aurobindo Pharma Ltd.
Date of Submission	October 7, 2008
PDUFA Goal Date	August 7, 2009
Proprietary Name	Zidovudine
Dosage forms / Strength	60 mg scored tablets
Proposed Indication(s)	Treatment of HIV-1 infection
Recommended:	Approval – twice daily dosing in children > 4 kg

b(4)

Comments:

The purpose of this addendum is to address the outcome and subsequent discussions regarding the June 3, 2009, PeRC meeting. 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. During the meeting, one committee member stated the proposed scored 60 mg tablet that disperses in water was not considered a new dosage form. A CMC representative was not present at the meeting and the final decision regarding PREA was deferred until further discussion within CMC. A subsequent review of the product by the PeRC subcommittee determined the scored 60 mg tablet that disperses in water is not considered a new dosage form; therefore, the application does not trigger PREA. Zidovudine is already available in tablet form and a new strength tablet that disperses in water with a score is not considered a new dosage form under PREA.

No additional review of this product is required by the PeRC (refer to Mr. George Greeley's email correspondence dated July 16, 2009). The appropriate pediatric documents will be amended accordingly and archived in DFS by Monica Zeballos, PharmD.

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/s/

Kimberly Struble
7/20/2009 06:17:34 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMORANDUM

Date	June 2, 2009
From	Kimberly Struble, PharmD Medical Team Leader Review
NDA/BLA #	22-294
Applicant	Aurobindo Pharma Ltd.
Date of Submission	October 7, 2008
PDUFA Goal Date	August 7, 2009
Proprietary Name	Zidovudine
Dosage forms / Strength	60 mg scored tablets
Proposed Indication(s)	Treatment of HIV-1 infection
Recommended:	Approval – twice daily dosing in children > 4 kg [redacted]

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Introduction:

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Aurobindo submitted a 505 (b) 2 application for zidovudine 60 mg scored tablets for twice daily [redacted] administration in HIV-1 infected children weighing 4 kg or greater. The tablets can be crushed and dissolved in water thereby providing dosing for the proposed population. No new pharmacokinetic, efficacy or safety data are included in the NDA. All data reviewed are based on publicly available information in the innovator label (Retrovir by GlaxoSmithKline) or based on literature references. This application is eligible for traditional approval because the US patent protection for zidovudine has expired. However, Aurobindo does not plan to market this formulation in the US. The 60 mg scored tablet formulation was developed for PEPFAR. A user fee waiver was granted for this application based on the commitment not to market in the US.

Recommendations and Conclusions:

I agree with the assessments made by Dr. Regina Alivisatos in the medical officer review. The review team compared Aurobindo's proposed twice daily [redacted] dosing for the 60 mg scored tablet to the approved Retrovir dosing based on mg/kg and body surface area (BSA). The twice daily doses by weight proposed by Aurobindo are similar to the approved twice daily doses for Retrovir. Deviations in the percent dose difference are expected for some weight groups and range from 16.7% lower to 25% higher compared to the twice daily dosing based on weight (mg/kg). Similar deviations are expected when compared to the approved twice daily dosing based on body surface area. As summarized in Dr. Alivastos review, adequate data exist to support the decreases and increases in ZDV dose and exposure. Therefore, I concur with the recommendation to approve zidovudine 60 mg scored tablets for use in HIV-infected children weighing at least 4kg. Twice daily dosing in children weighing less than 4 kg was not possible because children could be underdosed by as much as 35%.

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[redacted]

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The final labeling in PLR format is adequate for the safe and effective use in children. No post marketing requirements or commitments are needed with this application. A PREA waiver for children less than 6 weeks of age and less than 4 kg was granted. Dosing is not possible with this formulation and could result in children being underdosed by as much as 35%. Age appropriate innovator and generic syrup formulations are available.

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/s/

Kimberly Struble
6/15/2009 01:29:30 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	22-294
Submission Number	000
Submission Code	N
Letter Date	October 7, 2008
Stamp Date	October 7, 2008
PDUFA Goal Date	August 7, 2009
Reviewer Name	Regina Alivisatos, MD
Review Completion Date	May 30, 2009
Established Name	Zidovudine (ZDV)
(Proposed) Trade Name	N/A
Therapeutic Class	Antiviral
Applicant	Aurobindo Pharma Ltd.
Priority Designation	S
Formulation	60 mg tablet
Dosing Regimen	mg/kg
Indication	Treatment of HIV-1 Infection
Intended Population	Children 6 weeks – 18 years

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

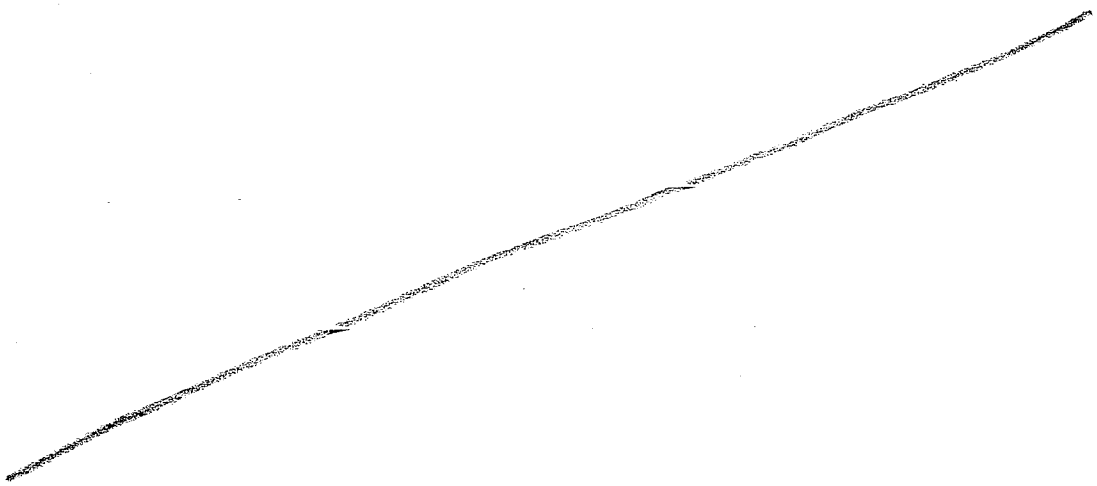
This executive summary contains the recommendations and summary of clinical findings for a new scored 60 mg zidovudine (ZDV) tablet manufactured by Aurobindo for pediatric use. The new scored tablet can be crushed and dissolved in water. This product was developed in response to the WHO Pediatric Antiretroviral Working Group as expressed in their 2007 report entitled "Preferred antiretroviral medicines for treating and preventing HIV infection in younger children". ZDV was designated a high priority drug for development in the form of 60 mg tablets. The advantages of a scored tablet which can be crushed and dissolved in water as compared to the available syrup formulation include the ability to provide more precise dosing in patients weighing greater than 10 kg. In addition such tablets would be easier to store and to transport as they take up less volume compared to the liquid formulation.

The Aurobindo 60 mg scored ZDV tablet formulation was initially developed for tentative approval under the President's Emergency Plan for AIDS Relief (PEPFAR); however, the US patent protection on ZDV has expired and therefore this formulation is being evaluated for a traditional approval. Based on this approval the Aurobindo 60 mg ZDV tablet can be marketed and distributed within the US; however, Aurobindo has no plans to market this formulation in the U.S..

The NDA was submitted as a 505 (b) 2 application and provides for dosing recommendations for children weighing 4 kg or greater using a twice [redacted] daily schedule and based upon mg/kg dosing calculations. No new efficacy or safety data are included. All data reviewed are based on publicly available information in the innovator label or based on literature references. b(4)

Aurobindo's proposed twice daily [redacted] the 60 mg scored tablet were compared to the approved ZDV dosing based on mg/kg and BSA. The twice daily doses by weight proposed by Aurobindo for the 60 mg scored tablet correlate reasonably well to the approved twice daily doses for the innovator product. Therefore adequate safety and efficacy data are available in the public domain to support approval of the 60 mg scored tablet and no data were required. Although there may be some deviations in the percent dose difference (range 16.7% lower to 25% higher compared to approved mg/kg dosing or from 20.3% lower to 23% higher compared to approved BSA dosing), these deviations are anticipated to occur infrequently and for short periods as they will mostly occur in very young patients who are in periods of rapid growth. Since dose-proportional increases in ZDV exposures are observed between oral (solution) doses of 90-240 mg/m^2 every six hours in children, an increase in dose in this range is proportionate to an increase in ZDV exposure. Therefore, the predicted deviations in exposures achieved with the proposed twice daily regimen are generally within the range of exposures achieved with the approved 300 mg twice daily adult dose for which there is a large amount of data supporting both efficacy and safety. Further the potential 16.7% - 20.3% decrease in total daily dose is not expected to adversely impact overall efficacy as numerous drug-drug interactions can lead to a similar or greater decrease in exposure without loss of efficacy (for b(4)

example the drug-drug interaction with ZDV and ritonavir where clinical data showed efficacy was not affected by the 25% reduction in ZDV exposures when coadministered with ritonavir) and without the need for changes in dosing recommendations.



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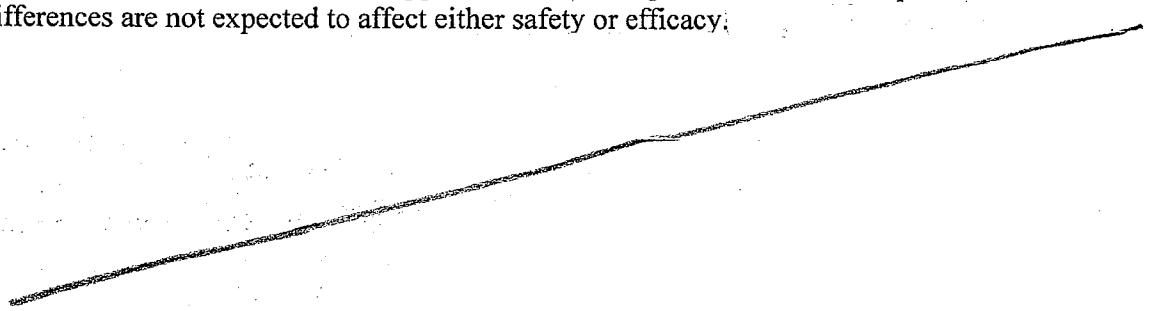
1.2 Risk Benefit Assessment

The scored 60 mg tablet which can be crushed and dissolved has the advantages of less volume, easier shipping and storage and possibly easier titration of doses in patients weighing greater than 10 kg. These advantages can be of great significance in the developing world as they may allow greater and more stable access (and thus increased adherence) to ZDV which remains a cornerstone of HAART regimens in pediatric patients.

There are few risks associated with the proposed twice daily dosing regimen where the dose and exposures range from 16.7% lower to 25% higher compared to approved mg/kg or from – 20.3% lower to 23% higher compared to approved BSA dosing with the innovator product. These differences are not expected to affect either safety or efficacy.



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1.3 Recommendations for Postmarketing Risk Management Activities

No specific Risk Management Activities were requested from the Applicant.

1.4 Recommendations for other Post Marketing Study Commitments

No Phase 4 Post Marketing commitments were requested.

2 Introduction and Regulatory Background

2.1 Product Information

Zidovudine is a thymidine analog that, after intracellular phosphorylation to zidovudine triphosphate metabolite, inhibits HIV-specific reverse transcriptase and terminates pro-viral DNA. The innovator ZDV product, Retrovir, was the first antiretroviral approved for the treatment of HIV infection and has been the cornerstone of HIV therapy in adults and children for approximately 20 years. With the original approval in March 1987, ZDV capsules were dosed 200 mg every four hours around the clock in adults. In 1989 the syrup formulation was approved and included dosing instructions for adults only. In 1990 use in pediatric patients three months – 12 years of age was approved. The original dosing regimen was 180 mg/m^2 every six hours (720 mg/m^2 day) not to exceed 200 mg every six hours. Subsequently the dosing in adults was revised to 100 mg every four hours (600 mg total daily dose) as monotherapy or 200 mg every eight hours in combination with zalcitabine and the pediatric dosing was amended to 6 weeks – 12 years of age at 160 mg/m^2 every eight hours (480 mg/m^2/day up to a maximum of 200 mg every 8 hours). In August 1994, ZDV received a new indication for prevention of mother to child transmission of HIV-1. This indication was based on a three part regimen including dosing of pregnant women > 14 weeks of pregnancy and during labor and deliver; followed by neonate dosing starting within 12 hours after birth and continuing through six weeks of age. In 1996 the package insert was updated to 600 mg per day in divided doses. The supplement in 1996 supported twice daily dosing regimen in adults based on a study in 158 patients comparing 100 mg every four hours to 300 mg twice daily. Until 2008 the innovator did not seek twice daily dosing in children despite the widespread off label use and recommendations by US and international treatment guidelines. However this changed in 2008 when the innovator sponsor submitted an NDA SLR application (NDA 19,910/S033) seeking a weight-based twice daily dosing regimen of ZDV in children weighing 4 kg or greater. This application led to an alignment of recommended pediatric dosing with ZDV worldwide with the new weight-based (mg/kg) twice daily recommendations providing for exposures between those achieved with previously approved three times daily BSA US guidelines and twice daily European guidelines.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, 32* antiretroviral distinct drug products (ARVs) are approved in the US for the treatment of HIV infection, some in multiple formulations and fixed drug combinations. Six classes of antiretroviral agents exist. The classes are based on the mechanism of action in the HIV life cycle: nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, entry inhibitors (CCR5 co-receptor antagonist), and HIV integrase strand transfer inhibitors.

The Department of Health and Human Services (DHHS) guidelines for use of antiretroviral agents in HIV-1 infected adults and adolescents do not include ZDV alone as a recommended treatment for HIV-1 infection but rather in conjunction with other antiretrovirals as part of HAART regimens.

A list of approved antiretroviral agents can be seen below:

Generic Name	Trade Name	Dosing Recommendations
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Abacavir (ABC)	ZIAGEN	300 mg PO BID or 600 mg QD
	TRIZIVIR (ABC/ZDV/3TC)	1 Tablet BID
	EPZICOM (ABC/3TC)	1 Tablet QD
Didanosine (DDI)	VIDEX EC	200 – 400 mg QD
Emtricitabine (FTC)	EMTRIVA	200 mg capsule QD or 240 oral solution QD
	ATRIPLA (FTC/EFV/TDF)	1 Tablet QD
	TRUVADA (FTC/TDF)	1 Tablet QD
Lamivudine (3TC)	EPIVIR	1500 mg BID or 300 mg QD
	COMBIVIR (3TC/ZDV)	1 tablet BID
	(see above for Epzicom and Trizivir)	
Stavudine (d4T)	ZERIT	30 – 40 mg BID
Tenofovir Disproxil Fumarate (TDF)	VIREAD	1 tablet QD)
	(see above for Atripla and Truvada)	
Zidovudine (AZT, ZDV)	RETROVIR	200 mg TID or 300 mg BID
	(see above for Combivir Trizivir)	
Non Nucleoside Reverse Transcriptase Inhibitors		
Delavirdine (DLV)	RESCRIPTOR	400 mg TID
Efavirenz (EFV)	SUSTIVA	600 mg QD
	(see above for Atripla)	
Etavirene (ETR)	Intelence	200 mg BID
Nevirapine (NVP)	VIRAMMUNE	200 mg QD x 14 days followed by 200 mg BID
Protease Inhibitors		
Atanazavir (ATV)	REYATAZ	400 mg Qd TN or with RTV (300/100) in TE
Darunavir (DRV)	PREZISTA	800 DRV/100 RTV QD TN or 600/100 BID TE
Fosamprenavir (FPV)	LEXIVA	1400 BID with or w RTV 100 – 200 mg QD or 700/100 BID
Indinavir	CRIXIVAN	800 mg q 8 hours
Lopinavir/Ritonavir (LPV/r)	KALETRA	400/100 BID or 800/200 QD 0r 600/150 with EFV
Nelfinavir (NFV)	VIRACEPT	1250 mg BID or 750 mg TID
Ritonavir (RTV)	NORVIR	600 mg q12 or 100- 400 QD in divided doses as PK enhancer
Saquinavir (SQV)	INVIRASE	SQV/RTV 1000/100 BID
Tipranavir (TPV)	APTIVUS	TPV/RTV 500/200 BID
Fusion Inhibitors		
Enfuviritide (T20)	Fuzeon	90 mg SQ BID
CCR5 Antagonists		
Maraviroc (MVC)	SELZENTRY	150 or 300 or 600 mg BID
Integrase Inhibitors		
Raltegravir	ISENTRESS	400 mg BID

2.3 Availability of Proposed Active Ingredient in the United States

Zidovudine is marketed in the US by the innovator sponsor, GSK as Retrovir® (Zidovudine or ZDV) for use in both adults and pediatric HIV-1 infected patients and is available for oral use as

100 mg capsules, 300 mg tablets, and a 10 mg/kg syrup. The efficacy and safety of ZDV have been extensively evaluated in previous NDA submissions including:

- Retrovir® Capsule NDA 19-655 AP March 19, 1987
- Retrovir® Syrup NDA 19-910 AP September 28, 1989
- Retrovir® Infusion IV NDA 19-951 AP March 19, 1987
- Retrovir® Tablet NDA 20-518 AP December 19, 1995

As patent protection has expired the generic formulations listed below are also available.

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
ZIDOVUDINE (ANDA # 074047)	CAPSULE; ORAL	100MG	None (Tentative Approval)	BARR
ZIDOVUDINE (ANDA # 076844)	TABLET; ORAL	300MG	Prescription	ROXANE
ZIDOVUDINE (ANDA # 077267)	TABLET; ORAL	300MG	Prescription	AUROBINDO
ZIDOVUDINE (ANDA # 077268)	SYRUP; ORAL	50MG/5ML	Prescription	AUROBINDO
ZIDOVUDINE (ANDA # 077327)	TABLET; ORAL	300MG	Prescription	RANBAXY
ZIDOVUDINE (ANDA # 077981)	SYRUP; ORAL	50MG/5ML	Prescription	CIPLA LTD
ZIDOVUDINE (ANDA # 078128)	CAPSULE; ORAL	100MG	Prescription	AUROBINDO PHARMA LTD
ZIDOVUDINE (ANDA # 078349)	CAPSULE; ORAL	100MG	Prescription	CIPLA LTD
ZIDOVUDINE (ANDA # 078922)	TABLET; ORAL	300MG	Prescription	MATRIX LABS LTD
ZIDOVUDINE (ANDA # 090092)	TABLET; ORAL	300MG	Prescription	HETERO DRUGS

2.4 Important Safety Issues With Consideration to Related Drugs

Zidovudine was the first antiretroviral approved for the treatment of adults and children with HIV infection and AIDS. Published data on the use of zidovudine in pediatric patients are less extensive than the available literature in adults but the pediatric safety and efficacy data are similar to the reported adult data.
The following adverse reactions are described in the **Boxed Warning** and/or **Warnings and Precautions** section(s) of labeling:

• Hematologic toxicity, including neutropenia and anemia
• Symptomatic myopathy
• Lactic acidosis and severe hepatomegaly with steatosis

• Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C.

The most commonly occurring adverse events in adults and in children are from the GI tract including nausea and vomiting. Laboratory abnormalities that occur frequently include anemia, granulocytopenia, thrombocytopenia, and increased ALT and AST.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the 2008 DHHS HIV-1 Pediatric Treatment Guidelines dated July 29, 2008, ZDV remains an integral component of some of the preferred and alternative dual background NRTI regimens that comprise HAART along with other ARV classes. Current dosing recommendations exist for pediatric patients as young as six weeks of age or with a minimum weight of 4 kg. The innovator product is supplied as an age appropriate syrup or as a 300 mg tablet for oral use. The Aurobindo 60 mg scored tablet has the potential to simplify dosing in pediatric patients especially those in areas where it is difficult to ship and maintain liquid formulations. The approved ZDV twice daily mg/kg dosing recommendations for children ages 6 weeks – 18 years of age or weighing from 4 – 30 kg can be seen in the following table:

Recommended Pediatric Dosage of RETROVIR

Body weight (kg)	Total Daily Dose	Dosage regimen and Dose	
		BID	TID
4 to < 9 kg	24 mg/kg/day	12 mg/kg	8 mg/kg
≥ 9 - < 30 kg	9 mg/kg/day	9 mg/kg	6 mg/kg
≥ 30 kg	300 mg	300 mg	200 mg

This submission includes no new efficacy or safety information. This is a 505 (b) 2 NDA and provides for dosing recommendations for children weighing 4 kg or greater with a scored, 60 mg tablet using a twice[redacted] daily schedule and based upon mg/kg dosing calculations. The tablet can be crushed and dispersed in water allowing for ease of administration in patients who are not able to swallow a solid oral formulation. All data reviewed are based on publicly available information in the innovator label or on literature references. There was no pre-submission regulatory activity specific to this submission. b(4)

The safety and efficacy of ZDV as part of a highly active antiretroviral therapy (HAART) regimen is supported by previously conducted adequate and well-controlled studies. Furthermore, ZDV has also been evaluated in open-label, single-arm or comparative pediatric clinical trials during pediatric development programs. Safety at the recommended pediatric doses has been well-established in clinical trials and postmarketing experience of the innovator product.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

As no clinical studies were submitted, no audits were requested.

3.2 Compliance with Good Clinical Practices

No studies were provided for review in this 505 (b) 2 submission.

3.3 Financial Disclosures

As no studies were performed with the ZDV 60 mg tablet formulation; therefore, there was no need for financial disclosure forms to be submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See chemistry review regarding stability of the proposed formulation.

4.2 Clinical Microbiology

No new clinical virology data were submitted with this application.

4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology data were submitted with this application.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

See 4.4.2

4.4.2 Pharmacodynamics

Zidovudine (ZDV) is a synthetic analog of the naturally-occurring nucleoside thymidine and has no intrinsic anti-HIV activity; it must first be converted intracellularly to its triphosphate form by the action of thymidylate kinase and non-specific kinases. Two primary mechanisms of action of ZDV triphosphate have been identified. First, the compound competes with naturally-occurring thymidine triphosphate for RNA-directed DNA polymerase (reverse transcriptase) resulting in decreased intercellular levels of this thymidine triphosphate. When ZDV triphosphate is

incorporated into a growing pro-viral DNA chain, the lack of 3' hydoxy group prevents the formation of the 5' to 3' phosphodiester linkage required for DNA chain elongation and viral growth is terminated.

ZDV is active *in vitro* against human and animal retrovirus. The *in vitro* activity of ZDV against laboratory and clinical isolates of HIV has been assessed in lymphoblastic and monocytic cell lines, and peripheral blood lymphocytes. The 50 and 90% inhibitory concentrations (IC50 and IC90) were 0.003 to 0.013 mg/L and 0.03 to 0.13 mg/L, respectively.

The prevalence of zidovudine-resistant strains of HIV in newly diagnosed treatment-naive individuals was shown to be between 5% and 10%. High-level resistance to ZDV requires the stepwise accumulation of mutations in the HIV-encoded reverse transcriptase at codons 41, 67, 70, 210, 215 and 219. In one study of 112 zidovudine-treated HIV-infected children who had experienced a median 30 months of ZDV monotherapy, 16% of the HIV isolates from these children were wild type while the remaining 84% contained ZDV -associated resistance mutations.

Nucleoside analogs can interfere with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction. mitochondrial toxicity is associated with the accumulation of ZDV monophosphate.

4.4.3 Pharmacokinetics .

In children over the age of five to six months, the pharmacokinetic profile of ZDV is similar to that in adults. ZDV is well absorbed from the gut and, at all dose levels studied; its bioavailability was 60 to 74% with a mean of 65%. Cmax levels were 4.45 micromole (1.19 micrograms/ml) following a dose of 120 mg/m^2 and 7.7 micromole (2.06 micrograms/ml) at 180 mg/m^2 (using ZDV oral solution). With intravenous (i.v.) dosing, the mean terminal plasma half-life and total body clearance were 1.5 h and 30.9 mL/min/kg respectively.

5 Sources of Clinical Data

No clinical data were submitted in support of this 505 (b) 2 application.

5.1 Tables of Clinical Studies

Not applicable

5.2 Review Strategy

5.3 Discussion of Clinical Pharmacology and Dosing Issues

The doses proposed by the Applicant for the scored 60 mg ZDV tablet correlate to the following mg twice daily doses:

Aurobindo Proposed Twice Daily Regimen:

Weight of Child (kg)	Number of tablets twice daily	Total Daily Dose (mg)
4 to 6	1	120
6.1 to 11	1.5	180
11.1 to 14	2	240
14.1 to18	2.5	300
18.1 to 22	3	360
22.1 to 25	3.5	420
25.1 to 28	4	480

NOTE: Aurobindo did not provide twice daily dosing recommendations for pediatric subjects weighing greater than 28 to less than 30 kg. As noted below, the innovator recommended dose for subjects weighing 30 kg or greater is 300 mg twice daily which is the same as the approved adult dose.

Dosing recommendations for the innovator zidovudine syrup 10 mg/mL for twice daily dosing are as follows:

Innovator Approved mg/kg BID Dosing regimen

4- < 9 kg	9-29.9 kg	> or = 30 kg
12 mg/kg BID	9 mg/kg BID	300 mg BID

The approved BSA based dose for the innovator product is 240 mg/m^2 twice daily (BID).

The following table generated by the Agency Clinical Pharmacology Review Team provides comparisons of the Applicant proposed two times daily regimen and the approved weight based and BSA based regimens.

Comparison Aurobindo and Innovator Twice Daily Dosing (mg/kg and BSA based) per FDA Clinical Pharmacology

	Innovator	Aurobindo	% Diff. wt-based		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.)	BSA	
**2.6	(31)	30	**-3.2**		42		-28.6
**3	(36)	30	**-16.7**		46		-34.8
4	48	60	**25.0**		54	0.227	10.1
5	60	60	0.0		64	0.267	-6.4
6	72	60	-16.7		73	0.303	-17.5
6.1	73.2	90	**23.0**		73	0.305	**23.0**
7	84	90	7.1		80	0.335	11.9
8	96	90	-6.3		88	0.367	2.2
9	81	90	11.1		96	0.402	-6.7

10	90	90	0.0		104	0.433	-13.4
11	99	90	-9.1		113	0.471	-20.3
11.1	99.9	120	**20.1**		113	0.473	5.8
12	108	120	11.1		123	0.511	-2.1
13	117	120	2.6		133	0.553	-9.7
14	126	120	-4.8		142	0.590	-15.2
14.1	126.9	150	**18.2**		142	0.591	5.7
15	135	150	11.1		151	0.631	-0.9
16	144	150	4.2		160	0.667	-6.3
17	153	150	-2.0		168	0.699	-10.6
18	162	150	-7.4		176	0.734	-14.8
18.1	162.9	180	10.5		177	0.735	2.0
19	171	180	5.3		183	0.763	-1.7
20	180	180	0.0		191	0.795	-5.7
21	189	180	-4.8		197	0.822	-8.8
22	198	180	-9.1		205	0.854	-12.2
22.1	198.9	210	5.6		205	0.856	2.2
23	207	210	1.4		213	0.887	-1.3
24	216	210	-2.8		219	0.913	-4.2
25	225	210	-6.7		227	0.946	-7.5
25.1	225.9	240	6.2		227	0.947	5.6
26	234	240	2.6		233	0.970	3.1
27	243	240	-1.2		240	0.999	0.1
28	252	240	-4.8		246	1.026	-2.5
29	261	---	---		253	1.053	---
30	300	---	---		258	1.074	---

*Doses in bold have >15% difference; red=underdose, black=overdose

** FDA generated modeling, not proposed by Applicant. The Agency CP Reviewer, Dr. Shirley LU, calculated the % difference in doses and exposures for pediatric patients weighing 2.6 and 3 kg respectively. These weights were used because they are the lowest weight where a 30 mg one half tablet could be administered. The resultant doses are approximately 28% and 35% lower than the BSA based doses of ZDV, that is patients could be under-dosed by as much as 35%. Given the availability of an age appropriate formulation, the innovator syrup, it was not deemed reasonable to extend dosing to patients weighing less then 4 kg with the Aurobindo 60 mg ZDV tablet.

The twice daily doses by weight proposed by Aurobindo for the 60 mg scored tablet correlate reasonably well to the approved twice daily doses for the innovator ZDV product: however, for some pediatric patients, especially those in the lowest weight band (4 – 6 kg) there could be as much as a 25% increase in the dose or achievable exposure (compared to the approved mg/kg recommendations). When the proposed doses are compared to the BSA based doses upon which current mg/kg dosing recommendations are based, the differences (increase) in anticipated exposures are not as great for any weight group. Based on BSA dosing, the anticipated exposures for the 4 kg group are increased by 10% as opposed to 25% when compared to the mg/kg recommendations. The only weight for which the proposed dose can lead to up to either a 23% increase or a 20.3 % decrease in exposure in comparison to mg/kg or BSA based dosing is the 6.1 kg group. Remarkably the percent difference in dose or achievable exposures for the 6 kg group could lead to a 16.7% decrease in ZDV exposures whereas the 7 kg group could lead to 7.1% increase in ZDV exposures Therefore, children weighing 6.1 kg are only exposed to higher ZDV exposures (23% increase) for a very short period given the rapid weight changes occurring at these ages (neonate – 3 months of age). The wide variations in exposures are most likely due to the low ZDV clearance at birth which increases substantially within the first two weeks of life

and is essentially the same as that seen in older pediatric patients after six weeks. Therefore, the predicted ZDV exposures are comparable to those achieved with the innovator product both in pediatric subjects dosed with either the mg/kg or BSA dosing recommendations or to those achieved with the approved adult dose of 300 mg twice daily. Thus similar efficacy and safety are expected with the proposed twice daily regimen.

The Applicant did not propose a twice daily dose for the greater than 28 kg to less than 30 kg weight band. According to WHO recommendations the dose for subjects weighing greater than 24.9 kg should be similar to the approved adult dose of 300 mg twice daily which correlates to five 60 mg tablets twice daily. The Agency proposes a dose of 4.5 tablets twice daily (270 mg twice daily) for patients weighing between 28.1 and less than 30 kg (For patients weighing 30 kg or greater, the adult dose of 300 mg twice daily should be used). . This proposed dose can be up to 16% greater that the innovator BSA dose and is not expected to lead to differences in safety.

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1 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical Review Section- A

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6 Review of Efficacy

Efficacy Summary

No new efficacy data were submitted in support of this application. The efficacy of ZDV is well-established in both adults and pediatric patients. The dose and exposures for the 60 mg scored tablet are similar to the innovator product. Although there may be some deviations in dose and in predicted exposures for the proposed twice daily mg/kg dosing recommendations for the scored tablet (range 16.7% lower to 25% higher compared to approved mg/kg dosing or from 20.3% lower to 23% higher when compared to approved BSA twice daily dosing), these deviations are anticipated to occur infrequently and for short periods as they will mostly occur in very young subjects who are in periods of rapid growth. Further the potential 16.7% - 20.3% decrease in total daily dose is not expected to adversely impact overall efficacy as numerous drug-drug interactions can lead to a similar or greater decrease in exposure without loss of efficacy (for example the drug-drug interaction with ZDV and ritonavir where clinical data showed efficacy was not affected by the 25% reduction in ZDV exposures when coadministered with ritonavir) and without the need for changes in dosing recommendations.

b(4)

6.1 Indication

No new Indication is sought with this NDA.

7 Review of Safety

Safety Summary

7.1 Methods

Many years of safety data with ZDV in adults and children at various doses and dosing regimens are available. The safety profile of ZDV is well-characterized and includes gastrointestinal intolerance and hematologic abnormalities, specifically anemia and neutropenia. Data from studies in children evaluating 640 -960 mg/m^2/day show no discernable safety differences compared to the approved BSA dosing regimen of 480 mg/m^2/day. It should again be stressed however that there is very limited safety information available for doses greater than 640 mg/ m^2/day.

ZDV twice daily in children has been used extensively off label worldwide for years and has been used in several clinical trials including CNAA3006 which supported approval for abacavir in children. No new or unexpected ZDV-associated adverse events have been reported in recent years. Overall an adequate safety database exists, including safety data at higher doses and exposures than the currently approved regimen to support approval in children where potentially a 25% increase in ZDV exposures is possible for a 4 kg child.

7.1.1 Clinical Studies Used to Evaluate Safety

No new safety data were submitted. All data summarized were based on literature references. Data from the historical pediatric studies (ACTG studies 152, 125, 300 and P53-04) as published in the literature were evaluated for safety to support the predicted up to 25% increases in exposures in children with the twice daily regimen. The safety data from these studies primarily support doses up to the US approved BSA dose of 480 mg/ m^2 total daily dose or the approved twice daily dosing regimens in children ages 6 weeks to 18 years of age or who weigh 4 kgs or greater. Limited safety data exists for dosing up to 960 mg/m^2 total daily dose (study P53-04). The safety from these trials are adequate to support the anticipated increases in exposures (up to 25%) with the Aurobindo scored 60 mg tablet when administered twice daily

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Table of Literature Based Studies Used to support Safety of Aurobindo Weight Based Twice Daily Dosing Regimens in Pediatric Patients

Study ID	ZDV Treatment Regimens	Patient #	Ages/Weight	TOTAL Daily Dose	Safety	Comments
ACTG 152	120 or 180 mg/m^2 q 6 DDI used both arms	120: n= 274 180 n = 276	3 mos- 18 yrs 15.5 ± 12.4 kg	480 or 720 mg/m^2	yes	TDD 720 mg/m^{2}exceeds proposed doses
G 128	90 or 180 mg/m^2 q6	90: n = 216 180: n = 208	3 mos. – 12 yrs 15.5 ± 12.4 kg	360 or 640 mg/m^2	yes	Comparable safety high and low dose, more neutropenia high dose.

						TDD 720 mg/m^{2}exceeds proposed doses
P53-04	80 or 160 mg/m^2 IV q6 followed by 120 or 240 mg/m^2 q6 PO Amended to 120 and 180 mg/m^2	36	6 mos. – 13 yrs 6.6 kg – 38.1kg	360. 480, 640 or 960 mg/m^2 (approx. 12 received 640 TDD)	yes	TDD 960 mg/m^{2}exceeds proposed doses
ACTG 300	ZDV/3TC ZDV/3TC + DDI ZDV + DDI	N = 236 N= 235 N = 125	42 d – 15 yrs	360 mg/m^2	Yes	More neutropenia ZDV versus liver for other groups

Safety support from the literature is summarized below.

PACTG300: 596 patients were enrolled, aged 42 days – 15 years. 236 received ZDV/3TC, 235 received ZDV/3TC and DDI and 125 received ZDV/DDI. Total ZDV dose was 480 mg/m^2 day (160 mg/m^2 three times a day).

The most commonly reported adverse experiences were neutropenia (5.3%), fever (4.9%), and hepatic abnormalities (4.3%). In the ddI treatment group there were 15 occurrences of elevated serum aspartate aminotransferase, alanine aminotransferase, or bilirubin levels versus five for the ZDV/3TC treatment group and four cases of pancreatitis in the ddI group compared to no cases of pancreatitis in the ZDV/3TC group. The incidence of gastrointestinal adverse events (nausea, vomiting, diarrhea) was numerically similar between the treatment groups. Neutropenia occurred more frequently in the ZDV/3TC group (17 cases versus eight for ddI). There were no significant differences between the two treatment groups with respect to the rate of Grade 4 (life-threatening) toxicities and no patient was judged to have a treatment-related toxicity as the major cause of death.

McKinney RE Jr, Johnson JM, Stanely K, Florence HY, Keller A, O'Donnell KJ, *et al.* A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy naive HIV-1 infection. ***J Pediatr* 1998, 133:500-508.**

PACTG 152: This study examined the use of ZDV 180 mg/m^2 every six hours, didanosine (ddI) 120 mg/m^2 every 12 hours, or a combination of reduced doses of both ZDV (120 mg/m^2 q6h) and ddI (90 mg/m^2 q12h) [Capparelli, 2003]. Patients ranged from three months to 18 years of age, with a mean (± SD) age of 45.2 ± 45.0 months and body weight of 15.5 ± 12.4 kg. In this study no association was found between ZDV exposures and growth failure, neuropsychological deterioration, HIV disease progression or death. Anemia was also more frequently observed in subjects receiving the higher ZDV dose compared to those receiving the lower dose of ZDV. Hemoglobin levels below 10 mg/dL occurred three times more frequently in subjects exposed to the higher ZDV dose and in infants (younger than two years of age), compared to those exposed to the lower dose . The incidence of severe anemia: however, was uncommon (five subjects), and no correlation with ZDV exposure or neutrophil counts was found; neutropenia occurred in 2% of participating patients. Finally, serious events that resulted in discontinuation of study therapy were uncommon among the three groups (2.9%).

Capparelli EV, Englund JA. Connor JD, JSpector SA, McKinney RE, Palumbo P, Baker CJ, and PACTG 152 Team. Population Pharmacokinetics and Pharmacodynamics of Zidovudine in HIV-Infected Infants and Children. J Clin Pharmacol 2003 43:133-140

PACTG 128: This study examined the use of ZDV 180 mg/m^2 every six hours compared to a reduced dose of ZDV (90 mg/m^2 q6h) [Brady, 1996]. Patients ranged from three months to 12 years of age, with a mean (± SD) age of 3.9 ± 2.8 years and body weight of 15.5 ± 12.4 kg. A total of 426 HIV infected pediatric patients were enrolled in the study and 424 were evaluable, with a median exposure to ZDV of 25 and 36 months in the high and low dose groups, respectively. No differences in baseline characteristics were seen; 74% and 81% of patients in the high dose vs. the low dose were still receiving full dose at 144 weeks. There were no differences in mortality, HIV disease progression or neurocognitive function between the two groups. Changes in CD4 cell counts and p24 antigen were also not significant. The safety profile of the two dosing regimens of ZDV was also comparable. Thirty-nine percent of patients reported a grade 3 or 4 hematologic toxicity and no significant differences were identified between the two groups. There was a higher frequency of grade 3 or 4 neutropenia in the higher ZDV dose group (68% versus 54%, p=0.9), but few patients discontinued therapy due to adverse events in the study. No differences in other laboratory abnormalities were observed. The authors concluded that the two groups (High dose vs. low dose) were comparable with respect to efficacy and safety and recommended that the lower dose be used in HIV infected children.

Brady M, McGrath, N, Brouwers P, et al. Randomized Study of the Tolerance and Efficacy of High- versus Low-Dose Zidovudine in Human Immunodeficiency Virus infected Children with Mild to Moderate Symptoms (AIDS Clinical Trial Group 128). *J Infect Dis* 1996; 173(5):1097-1106.

P53-04: This study evaluated the intravenous and oral pharmacokinetics of ZDV in pediatric HIV infected patients with AIDS or ARC. Patients originally received eight weeks of intravenous ZDV as one hour infusions every six hours at doses of either 80 or 160 mg/m^2 every six hours. This was followed by four weeks of oral dosing at 120 or 240 mg/m^2 every six hours. A subsequent protocol amendment allowed for indefinitely continued oral dosing, a reduction of the duration of intravenous therapy to four weeks, and the inclusion of an intermediate dose level of 120 mg/m^2 IV and 180 mg/m^2 orally. Serial blood samples were obtained around the first intravenous and oral dose predose through six hours post dose. Standard pharmacokinetic parameter estimates and measures of exposure were calculated for oral ZDV dosing using non-compartmental methods and pharmacokinetic relationships. A total of 36 patients were enrolled and ranged in age from six months to 13 years (mean 4.4 years), weighed from 6.6 to 38.1 kg (mean 15.8 kg), and had body surface areas from 0.3 to 1.2 m^2 (mean 0.64 m^2). A third of the subjects received a dose of 160 mg/m^2 every six hours. No substantial difference in tolerability of the different doses was reported.

Pharmacokinetics of zidovudine administered intravenously and orally in children with human immunodeficiency virus infection. Bslid et al J Pediatr, 1989 May;114(5):880-4

8 Overall Assessment

8.1 Conclusions

Efficacy: No new efficacy data was submitted in support of this application. As shown in section 5.3, the dose and exposures for the 60 mg scored tablet are similar to the innovator product. Although there may be some deviations in predicted exposures for the proposed twice daily mg/kg dosing recommendations for the scored tablet (range 16.7% lower to 25% higher compared to approved mg/kg dosing or from 20.3% lower to 23% higher when compared to approved BSA twice daily dosing), these deviations are anticipated to occur infrequently and for short periods as they will mostly occur in very young subjects who are in periods of rapid growth. Further the potential 16.7% - 20.3% decrease in total daily dose is not expected to adversely impact overall efficacy as numerous drug-drug interactions can lead to a similar or greater decrease in exposure without loss of efficacy (for example the drug-drug interaction with ZDV and ritonavir where clinical data showed efficacy was not affected by the 25% reduction in ZDV exposures when coadministered with ritonavir) and without the need for changes in dosing recommendations.

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[redacted]

Safety: The safety profile of zidovudine has been well-described in both adults and children. Twice daily dosing regimens have been used extensively worldwide and are well tolerated and safe. The exposures from the 60 mg scored tablet are anticipated to be similar to those of the approved in pediatric patients twice daily syrup regimen and therefore the safety is also expected to be similar despite the slight predicted increase in ZDV exposures of up to 25% in certain weight bands There is adequate literature support for the safety of the approved twice daily ZDV syrup regimen primarily from trials where ZDV doses of 480 - 640 mg/ m^2 total daily dose were used and which resulted in similar exposures to those predicted for the scored 60 mg tablet. No unexpected adverse events have been reported from these trials. Therefore, adequate safety data is available to support the proposed twice daily regimen with the scored 60 mg tablet.

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[redacted]

b(4)

8.2 Recommendation on Regulatory Action

b(4)

8.3 Recommendation on Postmarketing Actions

8.3.1 Risk Management Activity

Not applicable

8.3.2 Required Phase 4 Commitments

No postmarketing studies were recommended.

8.3.3 Other Phase 4 Requests

Not applicable

8.3.4 Pediatrics

See section 9

8.4 Labeling Review

See attached label. Final dosing recommendations are as follows:

Table 1. Recommended Pediatric Dosage of Zidovudine Tablets

Body 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)	2.5 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	4.5 tablets (270 mg)	4.5 tablets (270 mg)	540 mg
≥30	5 tablets (300 mg)*	5 tablets (300 mg)*	600 mg

*For recommended doses of 300 mg twice daily, the adult formulation (300 mg tablet) can be used.

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

8.5 Comments to Applicant

No comments to the applicant were required at the conclusion of this review.

9 Pediatrics

Because the Applicant is proposing a new tablet formulation PREA is triggered. The Applicant is requesting approval for pediatric patients weighing 4 kilograms or greater or who are older than 6 weeks of age. ZDV dosing for the treatment of HIV-1 infection is currently available for the approved age appropriate innovator product (syrup) for neonates as young as 6 weeks of age or who weigh 4 kg or greater. ZDV dosing recommendations are not available for treatment of HIV-1 infection in children between 4 - 6 weeks of age or for those who weigh less than 4 kg. (NOTE: DHHS pediatric treatment guidelines support early diagnosis of HIV and switching from ZDV chemoprophylaxis dosing to treatment dosing as soon as possible (at approximately 4 weeks).

The Agency Clinical Pharmacology Reviewer, Dr. Shirley Lu, calculated the percent difference ns doses and exposures for pediatric patients weighing 2.6 and 3 kg respectively. These weights were used because they are the lowest where a 30 mg one half tablet could be administered. The resultant doses are approximately 28% and 35% lower than the BSA based doses of ZDV, that is patients could be under-dosed by as much as 35%. Given the availability of an age appropriate formulation, the innovator syrup (and generic syrup formulations), it was determined not feasible to extend dosing to patients weighing less then 4 kg with the Aurobindo 60 mg ZDV tablet.

The Applicant has submitted a waiver request for pediatric dosing recommendations for HIV treatments in children less than 6 weeks of age or who weigh less than 4 kg (dated December 02.2008). Treatment studies in this age group are highly impractical and therefore it is recommended that the waiver be granted. If dosing of patients in this age group (4 – 6 weeks) is necessary, the preferred age appropriate, US approved formulation is available.

No additional pediatric requirements are needed at this time.

10 Appendices

10.1 Literature Review/References

Zidovudine A Review of its Use in the Management of Vertically-Acquired Pediatric HIV Infection Nila Bhana, Douglas Ormrod, Caroline M. Perry and David P. Figgitt Pediatr Drugs 2002; 4 (8): 515-553

Working Group on Antiretroviral Therapy and Medication Management of HIV-infected children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1 – 134. http://aidsinfo.nih.gov/content files/PediatricGuidelines.pdf

Saez-Llorens X, Nelson RP, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. Paediatrics 2001;107;4 *

Bergshoeff AS, Fraaij PLA, Verweij C, et al. Plasma levels of zidovudine twice daily compared with three times daily in six HIV-1-infected children. J Antimicrob Chemother
2004;54:1152-1154.

Rodman JH, Flynn PM, Robbins B, et al. Systemic pharmacokinetics and cellular pharmacology of zidovudine in human immunodeficiency virus type 1-infected women and newborn infants. J Infect Dis 1999;180:1844-1850.

Wintermeyer SM, Nahata MC, Brady MT, et al. Phosphorylated zidovudine concentrations in mononuclear cells in paediatric patients with human immunodeficiency virus infections. Pediatr AIDS HIV Infect 1997; 8(2):120-126.

Capparelli EV, Englund JA. Connor JD, JSpector SA, McKinney RE, Palumbo P, Baker CJ, and PACTG 152 Team. Population Pharmacokinetics and Pharmacodynamics of Zidovudine in HIV-Infected Infants and Children. J Clin Pharmacol 2003 43:133-140

Brady M, McGrath, N, Brouwers P, et al. Randomized Study of the Tolerance and Efficacy of High- versus Low-Dose Zidovudine in Human Immunodeficiency Virus infected Children with Mild to Moderate Symptoms (AIDS Clinical Trial Group 128). *J Infect Dis* 1996; 173(5):1097-1106.

Ruane PJ, Richmond GJ, DeJesus E, Hill-Zabala CE, Danehower SC, Liao Q, Johnson J, Shaefer MS; COD20002 Study Team. Pharmacodynamic effects of zidovudine 600 mg once/day versus 300 mg twice/day in therapy-naïve patients infected with human immunodeficiency virus. Pharmacotherapy. 2004 Mar;24(3):307-12

10.2 Advisory Committee Meeting

Not applicable

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/s/

Regina Alivisatos
6/15/2009 11:07:25 AM
MEDICAL OFFICER

Kimberly Struble
6/15/2009 01:24:30 PM
MEDICAL OFFICER