CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200732Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**200-732**	**Brand Name**	**None**
OCP Division (I, II, III, IV, V)	**DCP4**	**Generic Name**	**zidovudine**
Medical Division	**DAVP**	**Drug Class**	**NRTI**
OCP Reviewer	**Kellie Reynolds, Pharm.D.**	**Indication(s)**	**HIV**
OCP Team Leader	**Kellie Reynolds, Pharm.D.**	**Dosage Form**	**100 mg tablet**
Pharmacometrics Reviewer	**none**	**Dosing Regimen**	**Weight-based dosing**
Date of Submission	**4-23-2010**	**Route of Administration**	**oral**
Estimated Due Date of OCP Review	**5-2-2011**	**Sponsor**	**Matrix**
Medical Division Due Date	**5-2-2011**	**Priority Classification**	**S**
PDUFA Due Date	**2/23/2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology	**N/A**			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS	**X**			
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	**N/A**			
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**1**			

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Biowaiver requested
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?				Biowaiver requested
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Kellie Reynolds (no reviewer- TL review only for this application)

Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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/s/

KELLIE S REYNOLDS
02/10/2011

Clinical Pharmacology Team Leader Memo

NDA: 200-732
DRUG: Zidovudine tablets 100 mg (scored)
SPONSOR: Matrix Laboratories
STAMP DATE: 4/23/2010
TEAM LEADER: Kellie Schoolar Reynolds, Pharm.D.

Matrix submitted the current 505(b)2 NDA to gain approval of zidovudine 100 mg scored tablets. The application was submitted in response to the President's Emergency Plan for AIDS Relief (PEPFAR). The 100 mg scored tablets are intended for use in pediatric patients.

This application does not include an in vivo bioequivalence study report. Matrix's ANDA 78-922 (zidovudine 300 mg tablets) was approved by the Office of Generic Drugs based on demonstration of bioequivalence when Matrix's zidovudine 300 mg tablets were compared to US reference listed zidovudine tablets. The 100 mg tablets are proportional to Matrix's 300 mg zidovudine tablets, so Matrix requested a dissolution-supported biowaiver. The biowaiver request was reviewed by Dr. John Duan of the Office of New Drug Quality Assessment (ONDQA) biopharmaceutics group. Dr. Duan concluded the information was acceptable and granted the waiver. Dr Duan and the ONDQA chemistry reviewer, Dr. Maotang Zhou, determined that splitting scored tablets provides acceptable results, based on assessment of content uniformity and dissolution.

The only clinical pharmacology issue to address for the NDA was the appropriate dosing regimens for pediatric patients. Thus, the dosing recommendations proposed by Matrix were compared to the US approved doses in pediatric patients.

Matrix proposed the following doses for children who weigh at least 5 kg.

Table 1. Matrix proposed dosing recommendations of zidovudine 100 mg tablets

Weight	Dosage Regimen Using Scored 100 mg Tablets		Total Daily Dose
	AM Dose	PM Dose	
5 - 7 kg	0.5 tablet (50 mg)	1 tablet (100 mg)	150 mg
[redacted]			(b) (4)

Some of the proposed total daily doses are 30% less than the US approved dose (12 mg/kg twice daily for 4-<9 kg children; 9 mg/kg twice daily for children ≥9 kg). (See Table 3)

The scored 100 mg tablets accommodate dosing that is similar to the US approved dose, as indicated in Table 3. The FDA proposed doses are summarized in Table 2.

Table 2. FDA proposed doses of zidovudine 100 mg tablets

Weight	Dosage Regimen Using Scored 100 mg Tablets		Total Daily Dose
	AM Dose	PM Dose	
5 - <7 kg	0.5 tablet (50 mg)	1 tablet (100 mg)	150 mg
7 - <13 kg	1 tablet (100 mg)	1 tablet (100 mg)	200 mg
13 - <19 kg	1.5 tablets (150 mg)	1.5 tablets (150 mg)	300 mg
19 - <25 kg	2 tablets (200 mg)	2 tablets (200 mg)	400 mg
25 - <30 kg	2.5 tablets (250 mg)	2.5 tablets (250 mg)	500 mg
≥30 kg	Treat with recommended adult dose (300 mg twice daily)		

The following table supports the FDA recommended doses. The table displays the approved doses for the US reference listed drug, the doses proposed by Matrix, the doses proposed by FDA, and a comparison of the Matrix and FDA doses to the doses for the reference listed drug.

Table 3. Matrix and FDA proposed doses: comparison to US Reference Listed Drug

Wt (kg)	Approved doses for reference listed drug. (administered twice a day)		Dose proposed by Matrix		Ratio (Matrix/US approved) Total daily dose	Dose proposed by FDA		Ratio (FDA proposed/US approved) Total daily dose
	mg/kg	mg	Morning (mg)	Evening (mg)		Morning (mg)	Evening (mg)	
5	12	60	(b) (4)		(b) (4)	50	100	1.25
6	12	72				50	100	1.04
7	12	84				100	100	1.19
8	12	96				100	100	1.04
9	9	81				100	100	1.23
10	9	90				100	100	1.11
11	9	99				100	100	1.01
12	9	108				100	100	0.93
13	9	117				150	150	1.28
14	9	126				150	150	1.19
15	9	135				150	150	1.11
16	9	144				150	150	1.04
17	9	153				150	150	0.98
18	9	162				150	150	0.93
19	9	171				200	200	1.17
20	9	180				200	200	1.11
21	9	189				200	200	1.06
22	9	198				200	200	1.01
23	9	207				200	200	0.97
24	9	216				200	200	0.93
25	9	225				250	250	1.11
26	9	234				250	250	1.07
27	9	243				250	250	1.03
28	9	252				250	250	0.99
29	9	261				250	250	0.96

Matrix accepted the FDA proposal. A table similar to Table 2 is included in the product label. In addition, the label includes instructions for dispersing the tablets in water for patients who cannot swallow tablets.

All other label language is the same as the reference listed drug.

From a clinical pharmacology perspective, this NDA is acceptable.

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/s/

KELLIE S REYNOLDS
02/03/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**200-732**
Submission Date:	1/11/11
Generic Name:	Zidovudine
Formulation:	Tablets
Strength:	100mg
Sponsor:	Matrix
Reviewer:	John Duan, Ph.D.
Submission Type:	Response to information request

This NDA is for a lower strength (100mg) of Zidovudine tablets. The higher strength (300mg) was the subject of ANDA 78-922 approved on 2/14/2008. The current submission provides a response to an information request dated 12/8/2010 in which the dissolution profile comparisons between the half-tablets and between the half-tablets and the whole tablets were requested.

COMMENTS

1. The provided data support the similarity between the half-tablets and between the half-tablets and whole tablets.

RECOMMENDATION

The similarity between half-tablets and between half-tablets and the whole tablets have been demonstrated. The sponsor's response is acceptable.

No further action is indicated from a Biopharmaceutics perspective.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 200-732
Angelica Dorantes, Patrick Marroum, John Duan

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/s/

JOHN Z DUAN
01/12/2011

PATRICK J MARROUM
01/12/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**200-732**
Submission Date:	4/22/10
Generic Name:	Zidovudine
Formulation:	Tablets
Strength:	100mg
Sponsor:	Matrix
Reviewer:	John Duan, Ph.D.
Submission Type:	Initial NDA submission

The current submission is for a lower strength (100mg) of Zidovudine tablets. The higher strength (300mg) was the subject of ANDA 78-922 approved on 2/14/2008.

COMMENTS

1. The biowaiver can be granted for this lower strength based on its compositional similarity to the approved higher strength and the dissolution profile comparison between them.
2. The proposed dissolution specification Q=(b) (4) in 30 minutes using Apparatus II (paddle) with a rotation speed of 50rpm in 900mL of water at 37°C is acceptable.

RECOMMENDATION

The biowaiver can be granted. The dissolution methodology and specification proposed as follows is acceptable.

Apparatus:	USP II (Paddle)
Speed of Rotation:	50 RPM
Medium:	Water
Volume:	900 mL
Temperature:	37 ± 0.5°C
Acceptance Criterion	Q=(b) (4) in 30 minutes

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 200-732
Angelica Dorantes, Patrick Marroum, John Duan

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200732	ORIG-1	MATRIX LABORATORIES LTD	Zidovudine 100mg tablets

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/s/

JOHN Z DUAN
07/30/2010

PATRICK J MARROUM
08/02/2010