CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200732Orig1s000

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: Feb. 22, 2011

FROM: Jeff Murray, M.D.
Deputy, Division of Antiviral Products

SUBJECT: Deputy Director Memorandum for NDA 200-732
Zidovudine Tablets, 100 mg

TO: Division files

I. Background

The availability of a wide range of safe and effective antiretroviral drug products is hoped to facilitate a wider distribution of anti-HIV drugs to better meet the demands of the global HIV/AIDS pandemic. On Oct. 17, 2006 FDA published a guidance entitled "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV.`` The guidance encourages sponsors to develop various drug product versions of previously approved antiretroviral drugs and encourages sponsors to submit drug applications for these products to FDA for review. Although many antiretroviral drug product versions of previously approved antiretrovirals cannot be currently marketed in the US because of patent and exclusivity restrictions, FDA is able to review these products for quality, safety and efficacy and potentially grant a tentative approval. The President's Emergency Plan for AIDS Relief will consider procurement of products reviewed by FDA that have been granted approval or tentative approval. Such products may be distributed outside the US, depending on legal requirements in other countries.

Matrix previously received approval of Zidovudine Tablets, 300 mg under ANDA 78-922, reviewed by the Office of Generic drugs. Matrix submitted this 505 (b)2 NDA for a 100 mg scored tablet of zidovudine that is dispersible in water and intended for pediatric use. The dosing strength will allow dosing in children weighing at least 5 kg. Although syrup formulations are available for zidovudine, dispersible tablet formulations provide another option in situations where distribution and storage of a liquid is not feasible. Zidovudine is a commonly used nucleoside reverse transcriptase inhibitor that is combined with other drugs to form a complete HIV regimen.

II. Reviewers Findings

Chemistry, manufacturing, and controls (CMC) reviewer, Dr. Maotang Zhou, concurs with approval of Zidovudine 100 mg Tablets. The application provided adequate information on composition, manufacturing and packaging procedures, in-process controls, analytical methods and specifications that support the applicant's ability to consistently manufacture drug product meeting the desired strength, purity, potency and quality. As indicated in Dr. Zhou's review, the applicant's weight and assay results for the half-tablets (split on score line) demonstrate that dosing accuracy is not likely to be affected in the splitting process. The Office of Compliance made an "acceptable" site recommendation.

Please refer to Dr. Kellie Reynolds cross discipline team leader review for a description of the data supporting dosing recommendations for Zidovudine Tablets. Dr. Reynolds concurs with the approval of this product. The application does not include an in vivo bioequivalence study because a biowaiver was requested based on dose proportionality with the previously approved 300 mg tablets. Dr. John Duan from ONDQA Biopharmaceutics granted the biowaiver based on dissolution profiles.

Based on the reviews of the proposed dosing regimens and FDA's findings as included in the innovator's label, no significant changes compromising the efficacy and safety of zidovudine in pediatric patients are expected to occur with the use of this tablet formulation of zidovudine in children. The availability of a tablet formulation (for dispersion) for the pediatric population in resource limited countries will fulfill a medical need because the tablet formulation will be logistically easier to distribute and store in household settings in the developing world.

Also refer to the Labeling review prepared by Dr.David Araojo, who also concurs with the approval of this application.

III. Recommendations

Zidovudine Tablets, 100 mg, intended for use in pediatric patients weighing at least 5 kg should receive approval.

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Jeffrey S. Murray M.D., M.P.H.

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/s/

JEFFREY S MURRAY
02/22/2011

CROSS DISCIPLINE TEAM LEADER REVIEW

Date	February 9, 2011
From	Kellie Schoolar Reynolds, Pharm.D.
Subject	Cross Discipline Team Leader Review
NDA #	200-732
Applicant	Matrix Laboratories, Limited
Submission Stamp Date	April 23, 2010
PDUFA Goal Date	February 23, 2011
Proprietary Name / Established (USAN) names	Zidovudine
Dosage forms / Strength	100 mg scored tablet
Proposed Indication(s)	Treatment of HIV-1 infection
Recommended:	Approval

1. Introduction

This review summarizes the multi-disciplinary evaluation of the information submitted by Matrix Laboratories, Limited in NDA 200-732 to support approval of their 100-mg scored zidovudine tablet. Matrix submitted this 505(b)(2) application for zidovudine 100-mg scored tablets for twice daily administration in HIV-1 infected children who weigh 5 kg or greater. The tablets can be crushed and dispersed in water to allow dosing for the proposed population. The applicant did not conduct a bioequivalence study for this application; they requested a biowaiver because they obtained approval of a higher strength (300-mg) tablet. The Office of Generic Drugs granted approval of the 300-mg tablets on February 14, 2008 under ANDA 78-922. The 300-mg tablet was approved based on the results of fasted and fed bioequivalence studies that used Retrovir (zidovudine, GlaxoSmithKline) 300-mg tablets as the reference product. ONDQA biopharmaceutics group granted a biowaiver for the 100-mg tablet based on formulation proportionality and acceptable comparative dissolution data.

This application is eligible for full approval because the US patent protection for zidovudine expired on September 17, 2005. However, Matrix does not plan to market this formulation in the US. The 100-mg scored tablet formulation was developed for procurement by the President's Emergency Plan for AIDS Relief (PEPFAR) program. A user fee waiver was granted for this application based on the commitment not to market in the US.

2. Background

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 zidovudine product, Retrovir, was the first antiretroviral drug approved for the treatment of HIV-1 infection. Although originally administered as monotherapy, zidovudine is now administered only in combination with other antiretroviral drugs when used for the treatment of HIV-1.

Zidovudine is marketed as Retrovir® in the US by the innovator applicant, GlaxoSmithKline, for use in adult and pediatric HIV-1 infected patients. Retrovir is available for oral use as 100-mg capsules, 300-mg tablets, and 10-mg/mL syrup. The efficacy and safety of zidovudine were evaluated in previous New Drug Applications, including:

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

Zidovudine patent protection has expired and generic formulations are available. Some of the generic formulations were developed under the PEPFAR program. In addition, the Division of Antiviral Products has granted tentative approval to fixed dose combination products that include zidovudine. Some of these fixed dose products are formulations intended for pediatric patients. The tentative approvals were granted as part of the PEPFAR program.

Matrix developed the 100-mg scored tablet for use in pediatric patients. Although many drugs for use in pediatric patients are available as liquid formulations, the liquid formulations have a number of disadvantages in the developing world. The disadvantages include: storage difficulties, volumes required for dosing, palatability, and cost. A scored tablet that can be dispersed in water allows dosing in small patients who are dosed on a mg/body size basis and who cannot take a tablet.

3. CMC/Device

There are no unresolved CMC issues. I agree with conclusions reached by the CMC reviewer, Dr. Maotang Zhou.

Drug substance and drug product summary

The drug product is manufactured using drug substance manufactured by Matrix Laboratories Limited under DMF 17751. The DMF was reviewed and found adequate. The NDA includes some drug substance information. However, acceptability of the drug substance is based on review of the DMF. Satisfactory drug substance specifications are supplied. All limits conform to ICH Q3C. The analytical methods are described at a satisfactory level of detail.

The tablets contain 100 mg zidovudine and inactive ingredients that are compendial. This product is a scaled-down formulation of the zidovudine 300-mg tablet that was approved in ANDA 78-922. The current application provides and supports reasonable drug product specifications for appearance, identity, dissolution, content uniformity, related compounds, assay, loss on drying, and residual solvents. The analytical methods are the same as approved in ANDA 78-922. No novel impurities are identified.

Satisfactory analytical data are provided for 3 batches (b) (4) tablets. Tablets described in this application were made from the same blend as higher strength tablets that are bioequivalent to the Reference Listed Drug (Zidovudine tablets, 300-mg).

The drug product is packaged in white HDPE bottles containing 60 tablets. Each bottle is closed with an induction sealing liner and a white (b) (4) screw cap. (b) (4)

The applicant provided 12 months long term (30°C/75% RH) and 6 months accelerated(40°C/75% RH) stability data. The long term studies will be continued for 24 months and may be continued for 60 months if an extension of shelf life is to be requested. The proposed expiration dating period of 24 months when stored at 25°C is acceptable.

Data to support administration of half-tablets or tablet dispersion

An objective of this application was to support administration of drug product to children who are unable to swallow a tablet. In addition, doses for some weight groups require the administration of whole tablet(s) plus a half-tablet.

Dosing instructions are as follows:
If a child is unable to reliably swallow a zidovudine tablet, the method of preparation procedure listed below should be followed or the zidovudine syrup formulation should be prescribed.

1. Place the tablet(s) in container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet(s) break up into pieces small enough for the child to swallow. A spoon can be used to crush pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

Do not mix zidovudine tablet with any liquid other than water.

The chemistry reviewer indicated the wording above is acceptable.

In response to a request from the Agency, the applicant provided information to support use of half-tablets. As indicated in Dr. Zhou's review, the applicant's weight and assay results for the half-tablets (split on score line) demonstrate that dosing accuracy is not likely to be affecting in the splitting process. The weights of the tablets range from 46% to 54% (RSD of 4.4%). The loss to powder or small fragments ranges from undetectable to a maximum loss of 1% by weight, with an average loss of 0.3%

Manufacturing facilities
The drug substance (Zidovudine, USP) is manufactured by Matrix Laboratories, Limited, India at its (b) (4) facility. The drug product is manufactured at Matrix Laboratories, Limited (b) (4), Maharashtra, India. Packaging and release and stability testing occur at the manufacturing facility.

An overall recommendation of acceptable has been issued by Office of Compliance.

Environmental Assessment or Claim of Categorical Exclusion
The applicant claimed categorical exclusion.

4. Nonclinical Pharmacology/Toxicology

Not applicable. No new information submitted.

5a. Biopharmaceutics

Biowaiver
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.

ONDQA Biopharmaceutics granted the biowaiver based on the information summarized below. I agree with the assessment by the reviewer, Dr. John Duan.

The 300-mg and 100-mg tablets use a common blend, so the 100-mg tablet (b) (4) of all ingredients in 300-mg tablet.

Dissolution profiles were compared between the 300-mg and 100-mg tablets in water, the accepted dissolution medium for this product. Dissolution was (b) (4) for the 300-mg and 100-mg tablets at 15 minutes.

Dissolution method and specification

As indicated in Dr. Duan's review, the following dissolution methodology and specification 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

Split tablets

The applicant provided dissolution data to support use of half-tablets (split on score line). The data support similarity between half-tablets and whole tablets.

5b. Clinical Pharmacology

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
(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).

The scored 100-mg tablets accommodate dosing that is similar to the US approved dose. 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)		

Matrix accepted the doses proposed by FDA.

6. Clinical Microbiology

No new clinical virology data were submitted with this application.

7. Clinical- Efficacy

An efficacy review was not conducted for this NDA because the plasma drug exposure will be similar to the exposure following administration of the US approved reference listed drug.

8. Clinical- Safety

A safety review was not conducted for this NDA because the plasma drug exposure will be similar to the exposure following administration of the US approved reference listed drug.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The scored 100-mg tablet that disperses in water is not considered a new dosage form; therefore, the application does not trigger PREA.

11. Other Relevant Regulatory Issues

No regulatory issues are outstanding for this application.

12. Labeling

The label for this product is similar to the approved label for Retrovir. The applicant provided the label in PLR format, based on a request from the Agency. The label includes dosing instructions relevant to this formulation.

Section 2.0 of the label is presented below, because it is the label section that differs from the innovator label.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of HIV-1 Infection

Pediatric Patients (≥ 5 kg and ≥4 weeks of age): Healthcare professionals should pay special attention to accurate calculation of the dose of zidovudine, transcription of the medication order, dispensing information, and dosing instructions to minimize risk for medication dosing errors.

Prescribers should calculate the appropriate dose of zidovudine for each child based on body weight (kg) and should not exceed the recommended adult dose.

Before prescribing zidovudine tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a zidovudine tablet, the method of preparation procedure listed below should be followed or the zidovudine syrup formulation should be prescribed.

The recommended dosage in pediatric patients 4 weeks of age and older and weighing greater than or equal to 5 kg is provided in Table 1. Zidovudine syrup should be used to provide accurate dosage in pediatric patients who weigh less than 4 kg.

Preparation of Suspension:

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow, a spoon can be used to crush the pieces, if needed.
3. Drink the mixture within 1 hour.

4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX ZIDOVUDINE TABLET(S) WITH ANY LIQUID OTHER THAN WATER.

Table 1 Pediatric dosing for Zidovudine Tablets

Weight (kg)	Dosage Regimen Using Scored 100 mg Tablets		Total Daily Dose
	AM Dose	PM Dose	
5 - < 7	½ tablet (50 mg)	1 tablet (100 mg)	150 mg
7 - < 13	1 tablet (100 mg)	1 tablet (100 mg)	200 mg
13 - < 19	1.5 tablets (150 mg)	1.5 tablets (150 mg)	300 mg
19 - < 25	2 tablets (200 mg)	2 tablets (200 mg)	400 mg
25 - < 30	2.5 tablets (250 mg)	2.5 tablets (250 mg)	500 mg
≥30	To be treated with recommended adult dose		

13 Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  I concur with the assessments made by the review team and recommend approval of zidovudine 100-mg tablets for use in HIV-1 infected children.

- Risk Benefit Assessment

  The risk-benefit assessment is favorable because the twice daily dosing regimen provides a similar zidovudine dose as the approved regimens of the innovator product.

- Recommendation for Postmarketing Risk Management Activities

  No postmarketing risk management activities are required for this application.

- Recommendation for other Postmarketing Study Commitments

  No postmarketing study commitments are required for this application

- Recommended Comments to Applicant

  No additional comments to convey to the applicant.

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/s/

KELLIE S REYNOLDS
02/10/2011