CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-154

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Antiviral Products

Application Number: 22-154

Name of Drug: TYZEKA (telbivudine) Oral Solution

Applicant: Novartis Pharmaceuticals Corporation

Material Reviewed:

Submission Date(s): April 27, 2009

Type of Labeling Reviewed: WORD AND PDF

Background and Summary

This new drug application approves TYZEKA (telbivudine) oral solution for the treatment of chronic hepatitis B (CHB) in adult patients with evidence of viral replication and active liver inflammation; and CHB patients with renal impairment who may require dose reduction. This new drug application provides for labeling revisions to the 1)DOSAGE AND ADMINISTRATION, 2)DOSAGE FORMS AND STRENGTHS, 3)DESCRIPTION/HOW SUPPLIED, STORAGE AND HANDLING SECTION of the Full Prescribing Information and the 4)Medication Guide.

The submission included content of labeling in accordance with the Physician's Labeling Rule (submitted February 27, 2009 and April 27, 2009) and was submitted electronically in SPL. During the review of this NDA (22-154), a labeling supplement (S-002) for NDA 22-011 (Tyzeka tablet) was submitted April 27, 2009 to update the Tyzeka tablet label with the changes made in this NDA (22-154). Tyzeka tablet and oral solution will consist of one shared label.

Review

Updates to Labeling include the following:

Full Prescribing Information

1. The following changes were made to the DOSAGE AND ADMINISTRATION SECTION:

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

Conclusions

It was conveyed to the applicant that labeling is acceptable, and an approval letter was sent.

See electronic signature
Kenny Shade, JD, BSN
Senior Regulatory Health Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kenny Shade
4/30/2009 12:50:25 PM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 20, 2009
To:	Debra Birnkrant, M.D., Division Director **Division of Anti-viral Products (DAVP)**
Through:	Claudia Karwoski, PharmD, Director (Acting) **Division of Risk Management** Jodi Duckhorn, M.A., Team Leader **Division of Risk Management**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide and Patient Instructions for Use) and Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Tyzeka (telbivudine) Oral Solution
Application Type/Number:	NDA 22-154
Applicant/sponsor:	Novartis Pharmaceuticals
OSE RCM #:	2008-1075

1 INTRODUCTION

This review is written in response to a request from the Division of Antiviral Products (DAVP) for the Division of Risk Management to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

Since the Tyzeka (telbivudine) tablet formulation was approved in 2006, the Agency has become aware of the development of peripheral neuropathy, in some cases resulting in motor weakness, pain, sensory deficits and/or difficulty walking in patients taking Tyzeka. Residual neurologic deficits have been reported in patients when Tyzeka was continued after the development of neuropathy symptoms.

FDA has determined that Tyzeka (telbivudine) Tablets and Oral Solution pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Tyzeka (telbivudine) Tablets and Oral Solution. FDA has determined that Tyzeka (telbivudine) is a product with a serious a significant public health concern that meets one of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Tyzeka (telbivudine) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use.

2 MATERIAL REVIEWED

- Draft Tyzeka (telbivudine) Oral Solution Prescribing Information (PI) submitted on February 27, 2009. This includes the currently approved labeling for Tyzeka (telbivudine) Tablets.
- Draft Tyzeka (telbivudine) Oral Solution Medication Guide (MG) submitted on February 27, 2009. This includes the currently approved MG for Tyzeka (telbivudine) Tablets.
- Proposed Tyzeka (telbivudine) Risk Evaluation and Mitigation Strategy (REMS), submitted on February 27, 2009 for NDA 22-154. This includes the currently approved REMS for Tyzeka (telbivudine) Tablets.

3 BACKGROUND

Novartis submitted a New Drug Application (NDA# 22-154) for Tyzeka (telbivudine) Oral Solution on December 21, 2007. Novartis' NDA for Tyzeka Tablets (NDA# 22-011) was approved on October 25, 2006. Tyzeka Tablets is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. The applicant proposes the same indication for their oral solution formulation.

DRISK previously reviewed the Tyzeka (telbivudine) REMS and MG on January 8, 2009. The REMS and MG were approved for Tyzeka Tablets on January 23, 2009 with approval of the supplemental NDA 22-011/S-001. The NDA for the oral solution (NDA# 22-154) was under review at that time, but was not approved at that time due to other approvability issues.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to provide FDA with new authorities to require applicants of approved drugs to develop and comply with REMS section 505-1 of the FDCA if FDA finds that a REMS is necessary to ensure

that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

DAVP informed the Applicant during a teleconference on October 14, 2008, that a REMS is necessary for Tyzeka (telbivudine) tablets. The sponsor was also sent a Complete Response letter for Tyzeka oral solution on October 21, 2008, citing deficiencies in the application and outlining the requirements of the REMS submission. The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS, as with the Tablet formulation.

The Applicant submitted a proposed modification to the REMS for Tyzeka (telbivudine) Oral Solution on February 27, 2009.

4 DISCUSSION

4.1 MEDICATION GUIDE

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG and Patient Instructions for Use submitted by the Applicant has a Flesch Kinkaid grade level of 9.1, and a Flesch Reading Ease score of 53.4%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). Our revised MG has a Flesch Kinkaid grade level of 5.8 and a Flesch Reading Ease score of 75.2%.

In our review of the MG and Patient Instructions for Use, we have:

- limited our review to the identified changes in the PI, MG, and REMS documents
- simplified wording and clarified concepts where possible,
- ensured that the MG and Patient Instructions for Use are consistent with the PI,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4.2 PROPOSED REMS

The applicant's proposed REMS is unchanged from the REMS approved for Tyzeka NDA 22-011 on January 23, 2009, with the exception of the addition of the NDA 22-154. The proposed REMS includes the following:

a. Goal

The Applicant has proposed the following REMS goal:

1. To increase patient awareness of the potential for peripheral neuropathy to occur with Tyzeka treatment.
2. To raise patient awareness of the increased risk of developing peripheral neuropathy when Tyzeka is used in combination with pegylated interferon alfa-2a

b. REMS elements

- Medication Guide: The proposed REMS states that the Applicant will include a Medication Guide with each Tyzeka finished package. Medication Guides will be included in each carton containing a bottle of Tyzeka; there will be instructions on the carton and container label to the pharmacist instructing that the Medication Guide be distributed with the dispensed product.

  Novartis will conduct patient surveys to confirm distribution and understanding of the Medication Guide.

- The Timetable for Submission of Assessments is as follows:
  - 1st assessment: 18 months after approval (July 2010)
  - 2nd assessment: 3 years after approval (January 2012)
  - 3rd assessment: 7 years after approval (January 2016)

The timetable for submission of assessments is unchanged and will follow the schedule that was approved with the initial approval of the REMS for Tyzeka Tablets.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the Applicant's proposed REMS for Tyzeka (telbivudine) is acceptable with the addition of the NDA# 22-154.

We have the following comments on the proposed REMS:

1. We remind the Applicant of their requirement to comply with 21 CFR 208.24
   - A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
     "Dispense the enclosed Medication Guide to each patient." or
     "Dispense the accompanying Medication Guide to each patient."
   - Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled

prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:

- A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
- A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

2. The Applicant's proposed timetable for assessments (18 months, 3 years, and 7 years) is acceptable. The Applicant should submit for review a detailed plan to evaluate patients' understanding about the safe use of Tyzeka (telbivudine) at least 2 months before they plan to conduct the evaluation. The submission should include:
    - All methodology and instruments that will be used to evaluate the patients' understanding about the safe use of Tyzeka (telbivudine). This should include, but not be limited to:
        - Sample size and confidence associated with that sample size
        - How the sample will be determined (selection criteria)
        - The expected number of patients to be surveyed
        - How the participants will be recruited
        - How and how often the surveys will be administered
        - Explain controls used to minimize bias
        - Explain controls used to compensate for the limitations associated with the methodology
    - The survey instruments (questionnaires and/or moderator's guide).
    - Any background information on testing survey questions and correlation to the messages in the Medication Guide.

3. We recommend DAVP include in the approval letter a reminder of the Applicant's responsibility to provide the information needed (methodology) to assess the effectiveness of the REMS as stated above, including:
    a. An evaluation of patients' understanding of the serious risks of Tyzeka (telbivudine)
    b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
    c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

We have the following comments on the proposed Medication Guide:

4. The Patient Instructions for Use were relocated at the end of the Medication Guide.

[ ] b(4)

The applicant should label each figure and reference the figures in the text of the Patient Instructions for Use as appropriate.

5. In the description of the supplies needed to take a dose of Tyzeka Oral Solution, the applicant should clarify what is meant by [redacted] b(4)

6. [redacted] b(4)

7. The applicant should magnify the picture which demonstrates the patient pouring and measuring their dose of medicine, to show the dose matching up with one of the lines on the dosing cup.

Please let us know if you have any questions.

20 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Mills
4/20/2009 03:44:15 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/20/2009 04:07:08 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
4/22/2009 08:04:24 AM
DRUG SAFETY OFFICE REVIEWER

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTIVIRAL PRODUCTS

NDAs: 22-011/S-001; 22-154
PRODUCT(s): TYZEKA® (telbivudine) oral solution and tablets
SPONSOR: Novartis
REVIEWER: Mary Singer, M.D., Ph.D.
DATE: September 9, 2008

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

Since TYZEKA® (telbivudine) tablets were approved in 2006 for the treatment of chronic hepatitis B virus (HBV) infection, we have become aware of the development of peripheral neuropathy, in some cases resulting in motor weakness, pain, sensory deficits and/or difficulty walking in patients taking TYZEKA® (telbivudine) tablets or the oral solution, which is a new drug application. This information is from safety reports from Study CLDT600A2406 and from postmarketing adverse event reports. This information was not available when TYZEKA® (telbivudine) tablets were granted marketing authorization for the treatment of chronic HBV infection. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of TYZEKA® (telbivudine) outweigh the risks.

A. The number of patients with chronic hepatitis B infection in the United States is estimated to be approximately 800,000 to 1.4 million.

B. Potential complications of untreated chronic HBV infection include cirrhosis, liver failure, hepatocellular carcinoma, need for liver transplantation, and death.

C. The use of TYZEKA® (telbivudine) has been shown to result in histological improvement in the liver, HBV DNA suppression to < 5 $\log_{10}$ copies/mL, with either loss of serum HBeAg, or normalization of ALT in the majority of patients receiving 52 weeks of treatment.

D. The optimal duration of therapy with TYZEKA® (telbivudine) has not been established, however, it has been studied for at least 52 weeks.

E. Known serious risks associated with the use of nucleoside analogues such as TYZEKA® (telbivudine) include life-threatening or fatal lactic acidosis and severe hepatomegaly with steatosis, severe acute exacerbations of hepatitis after discontinuation of treatment, and myopathy and/or myositis.

F. TYZEKA® (telbivudine) is not an NME. However, the oral solution is a new dosage form.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that TYZEKA® (telbivudine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of TYZEKA® (telbivudine). FDA has determined that TYZEKA® (telbivudine) is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, TYZEKA® (telbivudine).

The patient package insert for TYZEKA® (telbivudine) will be converted to a Medication Guide. The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kenny Shade
10/21/2008 02:59:09 PM
CSO

Debra Birnkrant
10/21/2008 03:04:02 PM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 17, 2008
To:	Debra Birnkrant, MD Division of Anti-Viral Products
Thru:	Linda Kim-Jung, PharmD, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Denise V. Baugh, PharmD, BCPS, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Tyzeka (Telbivudine) Oral Solution 20 mg/mL
Application Type/Number:	NDA# 22-154
Applicant/sponsor:	Novartis Pharmaceuticals
OSE RCM #:	2008-1074

CONTENTS

EXECUTIVE SUMMARY

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton labeling and container labels introduces vulnerability to confusion that could lead to medication errors. Specifically, the prominence of the established name is not commensurate with the prominence of the trade name, the statement of strength is not conducive to calculating the recommended dose for the oral solution, and the difference in recommended dosing for the oral solution versus the tablet in renally impaired patients must be brought to the attention of healthcare providers to avoid medication errors. Additionally, the graduations on the measuring device should be consistent with the recommended dosing such that there should only be graduations for 10 mL, 15 mL, 20 mL, and 30 mL. Furthermore, these graduations need to be clearly identified so that they are easy for the patient to read and to provide accurate measurements.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim to reduce the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anti-Viral Products, for assessment of the container label, carton and insert labeling for Tyzeka oral solution.

Additionally, DMEPA notes that the review division also consulted the Division of Pharmacovigilence (DPV) for a postmarketing safety review of Tyzeka. DPV presented the findings of the safety review to the review division on September 3, 2008.

1.2 REGULATORY HISTORY

Tyzeka 600 mg oral tablets were approved October 25, 2006 under NDA# 22-011. The Applicant now proposes an oral solution with concentration, 20 mg/mL.

1.3 PRODUCT INFORMATION

Tyzeka (telbivudine) is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. The recommended dose is 600 mg orally once daily, with or without food. This regimen is adjusted for renally compromised patients. It will be supplied as a 20 mg/mL oral solution in a 300 mL bottle.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the DMEPA medication error staff to conduct a label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

---

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container labels communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the U. S. Pharmacopeia-Institute of Safe Medication Practices (USP-ISMP) Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because DMEPA staff analyze reported misuse of drugs, DMEPA staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMEPA uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Sponsor submitted on December 21, 2007 the following labels and insert labeling for DMEPA review (see Appendix A and B for images):

- Container Label: 20 mg/mL, 300 mL bottle
- Carton Labeling: 20 mg/mL, 300 mL bottle
- Prescribing Information (no image)

A sample measuring device was sent to DMEPA on September 26, 2008.

2.1.1 Adverse Event Reporting System (AERS)

On August 1, 2008, the Division of Medication Error Prevention and Analysis conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors involving Tzeka oral tablets have been reported. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredient (telbivudine), trade name (Tyzeka) and the verbatim term 'Telbi%'.

Cases that did not describe a medication error were excluded from further analysis and the cases that did describe a medication error were categorized by type of error. We excluded the types of errors that would not logically translate to the new oral solution. We reviewed the cases within each category to identify contributing factors.

---

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

3.1.1 AERS Selection of Cases

The AERS search retrieved no medication error cases involving Tyzeka oral tablets that were thought to be relevant to the new oral solution.

3.1.2 General Comments

1. The established name does not have a prominence commensurate with the prominence of the trade name in accordance with CFR 201.10(g)(2).
2. As currently stated, the strength is "20 mg/1 mL". Since the recommended volume per dose for Tyzeka may range from 10 mL (200 mg) to 30 mL (600 mg), the manner in which the strength is stated is not conducive to calculating the correct amount of oral solution needed for treatment. Additionally, the number '1' before 'mL' can be misinterpreted as 10 mL. This presentation is problematic because obtaining the recommended doses of 200 mg, 300 mg, 400 mg or 600 mg may lead to an erroneous calculation by the patient or healthcare practitioner.
3. The measuring device (dosing cup) is made of a clear plastic material with clear numbers and it holds up to 30 mL which is graduated in 5 mL increments. The markings are illegible.

3.1.3 Package Insert Labeling

For renally impaired subjects in the Dosage and Administration Section (section 2.2), it is noted that the *dosing* for the oral solution changes with altered renal function, but it is the *frequency* that changes with the tablets for the same patient population. This discordance may cause confusion for the user and lead to medication errors because healthcare providers are more familiar with a one to one conversion between tablets and oral solution for drug products.

Additionally, the dosing information for renally impaired patients is presented differently in the Dosage and Administration section under 'Highlights of Prescribing Information' section versus the Dosage and Administration section under 'Full Prescribing Information' (Section 2.2). In the 'Highlights' section the dosing is given in milliliters whereas in the section titled 'Prescribing Information' this information is provided in milligrams. Stating the dose in milliliters as well as milligrams in both sections of the package insert will maintain consistency in presentation of information, assist in minimizing calculation errors and facilitate communication between healthcare practitioners as well as communicating with the patient.

4 DISCUSSION

The results of the Label and Labeling Risk Assessment found that the presentation of information appears to be vulnerable to confusion that could lead to medication errors. We specifically note that the established name lacks prominence, the statement of strength is not conducive to calculating the recommended dose, the graduations on the dosing cup do not coincide with the dosing recommendations, and the conversion between oral tablets and oral solution in renal failure patients may be problematic for patients and healthcare practitioners.

4.1.1 Prominence of the Established Name

We acknowledge that the established name is half the size of the trade name. However, the established name does not have a prominence commensurate with the trade name in accordance with 21 CFR

201.10(g)(2). As currently presented, the established name is stated in lighter weight font, italicized and written very closely together. This makes it less prominent and less noticeable on the label.

4.1.2 Statement of Strength

DMEPA notes that the statement of strength is presented as 20 mg/1 mL. As the smallest dose for this drug product will be 10 mL (200 mg) and the largest, 30 mL (600 mg), the statement of strength requires calculation to achieve the desired dose increasing the risk of miscalculations. Expressing the statement of strength as 100 mg/5 mL may minimize the potential for medication errors due to miscalculations. Although this presentation would still require calculation, we believe it to be an easier calculation and it is consistent with the expression of most oral solutions.

4.1.3 Dosing Cup

We further note that the graduations included on the 30 mL cup (5 mL increments) do not coincide with the dosing recommendations. For example, the lowest volume stated on the cup is 5 mL although this volume is not recommended in the dosing instructions. The Applicant has acknowledged this discrepancy in an e-mail dated October 1, 2008 to the review Division and they are assessing other options for the dosing cup. The ideal would be for the cup to only include graduations that correspond to the usual dosage section. No extraneous markings should be present.

The measuring device (dosing cup) is made of a clear plastic material with clear numbers making the volumes difficult to read. This presentation may cause dosing errors as a result. The graduations should be revised so that the markings are legible (e.g., black print).

4.1.4 Dosing for Renally Impaired Patients

For renally impaired patients the recommended dosing regimen for the tablets differs from the recommended dosing using the oral solution. We acknowledge that the reason for this discordance was that the oral solution was unavailable at the time the [redacted] tablet dosage form was approved and therefore the only option to address renal impairment dosing was to adjust the frequency. Despite this, the difference in dosing regimens is problematic because the standard of practice for clinicians is to use the same dose and frequency when converting between the tablet and the solution due to assumed equal bioavailability among these two dosage forms. Therefore, this conversion as presented is not intuitive. b(4)

To bring this discordance between these dosage forms to the attention of the healthcare professional, we propose adding a separate statement in section 2.2 and preceding the dosing table (Table 2-1) warning practitioners of this discrepancy when attempting to switch. This statement may be 'caution: the dose and frequency for the oral solution in renally compromised patients is not the same as with tablets. Please refer to the appropriate creatinine clearance for your patient and the desired dosage form in the following table to find your patient's correct regimen'.

Additionally we noted the provision of the dose for renally impaired subjects in *milliliters* in the 'Highlights of Prescribing Information' section and the same information provided in *milligrams* in Section 2.2 of the section titled 'Full Prescribing Information'. The dosing information should be presented consistently throughout the label and labeling to avoid confusion and dosing errors. If healthcare providers are required to calculate this information, it can lead to a potentially erroneous calculation which can easily be avoided with the provision of this information along with the volume in milliliters.

5 CONCLUSIONS AND RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, the established name should be more prominent, the statement of strength should be consistent with the recommended dosing, and the difference in recommended dosing for the oral solution versus the tablet in renally impaired patients should be brought to the attention of healthcare providers to avoid medication errors. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim to reduce the risk of medication errors.

Please forward Comments to the Applicant from Section 5.2 below.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Darrell Jenkins, OSE project manager, at 301-796-0558.

5.2 COMMENTS TO THE APPLICANT

A. All Container Labels and Carton Labeling

1. Increase the prominence of the established name such that it is commensurate with the prominence of the trade name taking into account all pertinent factors including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

2. As currently presented the strength is stated as 20 mg/1 mL. Since the recommended dose for Tyzeka is no less than 10 mL and no more than 30 mL, presentation of the statement of strength as 20 mg/1 mL is not conducive to calculating the amount of oral solution needed for treatment. DMEPA recommends expressing the statement of strength as 100 mg/5 mL which may minimize the potential for medication errors due to miscalculations. Although this presentation would still require calculation, we believe it to be an easier calculation and it is consistent with the expression of most oral solutions. Regardless of whether the statement of strength is changed as recommended, you are advised to delete the number '1' prior to 'mL' as this presentation can lead to misinterpretation of the strength as 20 mg/10 mL.

B. Measuring Device

The graduations on the measuring device should be consistent with the recommended dosing such that 10 mL, [redacted] 20 mL, and 30 mL are easy for the patient to read and to measure. Ensure the markings are legible on the dosing device and that all extraneous graduations are deleted. b(4)

C. Package Insert Labeling (Dosing of Renally Impaired Patients)

1. As the recommended regimen for the oral solution is different from the tablets, there is the potential for inappropriate conversion between the two dosage forms leading to toxicity or therapeutic failure. A precautionary statement should appear prior to the dose adjustment table in the package insert labeling to emphasize appropriate selection of the regimen given a specific creatinine clearance. For example, the statement may be, 'caution: the dose and frequency for the oral solution in renally compromised patients is not the same as with tablets. Please refer to the appropriate creatinine clearance for your patient and the desired dosage form in the following table to find your patient's correct regimen.'

2. To provide consistency, decrease the potential for calculation errors and to facilitate communication among healthcare providers, state the milligram and milliliter strength next to each other in the column titled 'oral solution dose' in Table 2-1.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Micromedex Integrated Index (http://weblern/)

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. Phonetic and Orthographic Computer Analysis (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for DMETS, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (http://weblern/)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. Division of Medication Error Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by DMETS from the Access database/tracking system.

7. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

8. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. U. S. Patent and Trademark Office website http://www.uspto.gov.

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (http://weblern/)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (http://weblern/)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. Stat!Ref (http://weblern/)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. Lexi-Comp (www.pharmacist.com)

A web-based searchable version of the Drug Information Handbook.

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Baugh
10/17/2008 02:27:08 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
10/17/2008 03:27:47 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/17/2008 04:17:14 PM
DRUG SAFETY OFFICE REVIEWER