CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-165

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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:	May 28, 2009
To:	Russell Katz, M.D., Director
	Division of Neurology Products
Through:	Claudia Karwoski, PharmD., Director (Acting)
	Division of Risk Management
	Jodi Duckhorn, MA, Team Leader
	Division of Risk Management
From:	Robin Duer, RN, MBA
	Patient Product Information Reviewer
	Division of Risk Management
Subject:	DRISK Review of Risk Evaluation and Mitigation Strategy
Drug Name(s):	CAMBIA (diclofenac potassium for oral solution)
Application Type/Number:	NDA 22-165
Applicant/sponsor:	Kowa Pharmaceuticals America, Inc.
OSE RCM #:	2008-1823

1 INTRODUCTION

This review is written in response to a request from the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) 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. Comments on the draft Medication Guide were sent to DNP in a separate memorandum dated May 13, 2009.

2 MATERIAL REVIEWED

- Diclofenac Potassium for Oral Solution Complete Response Letter including the FDAAA Risk Evaluation and Mitigation Strategy (REMS) request dated October 27, 2008
- Proposed Diclofenac Potassium for Oral Solution REMS submitted December 12, 2008

3 BACKGROUND

On September 27, 2007 the Agency received a new drug application (NDA) for diclofenac potassium powder sachet for oral solution for the treatment of acute migraine attacks with or without aura in adults. The original submission was from ProEthic, but as of September 1, 2008, ProEthic changed its name to Kowa Pharmaceuticals America, Inc. and assumed responsibility for all sales and marketing functions operating in the U.S. A Patient Package Insert (PPI) was submitted with the original application, and on October 7, 2008, DNP requested that DRISK review the proposed patient labeling. Additionally, DNP planned to inform the Applicant that a REMS submission was required for this NDA, and DNP requested that DRISK also review the pending REMS submission.

On October 27, 2008 the Agency issued a Complete Response (CR) letter for this NDA. That letter stated that DNP had determined that a REMS was necessary for diclofenac potassium for oral solution to ensure that the benefits of the drug outweigh the risks. Non-steroidal anti-inflammatory drugs, including diclofenac potassium for oral solution, are associated with numerous safety risks, including an increased risk of cardiovascular events and gastrointestinal toxicity. A template for the proposed REMS was included in the October 27, 2008 letter. The letter specified that the REMS should include a Medication Guide and a Timetable for Submission of Assessments. The REMS should specifically include an evaluation of:

- Patients' understanding of the serious risks of Diclofenac Potassium for Oral Solution
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

On December 12, 2008, Kowa Pharmaceuticals America, Inc. submitted their proposed REMS in response to the Agency's October 27, 2008 action letter. On April 22, 2009,

DNP informed DRISK that the proprietary name "CAMBIA" would be approved for this NDA, so the name CAMBIA will be used in this document.

4 PROPOSED REMS

The Applicant submitted a proposed REMS with the following goals and elements:

a. Goal

The Applicant has proposed the following REMS goals:

The primary goal of the REMS is to help ensure that an FDA approved Medication Guide/Patient Package Insert (MG/PPI) is provided to patients at the point of contact when they receive their medication.

The secondary goal of the REMS is to provide healthcare practitioners with sufficient materials within the Package Insert and the MG/PPI to assist them in communicating to patients the risks of using CAMBIA.

b. REMS elements

- Medication Guide: The proposed REMS states that a MG/PPI will be dispensed to patients with each CAMBIA prescription that is filled. Because the MG/PPI will be included as part of the secondary package for CAMBIA, Kowa Pharmaceuticals America, Inc. (Kowa) believes it has met the requirements of 21 CRF 208.24 for distribution and dispensing of the MG/PPI.

- The Timetable for Submission of Assessments is as follows:
    - 1st assessment: 18 months after approval
    - 2nd assessment: 3 years after approval
    - 3rd assessment: 7 years after approval

  Kowa will submit the final assessment reports within 60 days from the close of the above noted intervals.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the Applicant's proposed REMS for CAMBIA generally meets the statutory requirements outlined in 21 CFR 208 and in accordance with 505-1. See the appended CAMBIA (diclofenac potassium for oral solution) REMS proposal (Appendix A) for track changes corresponding to comments in this review. We have the following comments and recommendations on the proposed REMS:

1. Throughout the proposed REMS:

    - delete the proposed name "PRO-513" and insert the agreed-upon proprietary name "CAMBIA"

    - delete the terms "patient package insert" and "MG/PPI" and insert the term "Medication Guide"

2. Revise the REMS goal to more specifically address the risks associated with the use of CAMBIA as follows:

To inform patients about the serious risks associated with the use of CAMBIA, particularly the increased risk of cardiovascular events and gastrointestinal toxicity.

3. 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.

4. The Applicant should submit for review a detailed plan to evaluate patients' understanding about the safe use of CAMBIA (diclofenac potassium for oral solution) 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 CAMBIA (diclofenac potassium for oral solution). 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.

5. We recommend DNP 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 CAMBIA (diclofenac potassium for oral solution)
    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

Please let us know if you have any questions.

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

/s/

Robin E Duer
5/28/2009 08:57:20 AM
DRUG SAFETY OFFICE REVIEWER

Claudia-MG canned language left in per DMEPA, background info revised in memo, MG received after CR letter sent

Jodi Duckhorn
5/28/2009 08:58:50 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
5/29/2009 10:01:30 AM
DRUG SAFETY OFFICE REVIEWER

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:	May 13, 2009
To:	Russell Katz, MD, Director **Division of Neurology Products**
Through:	Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Robin Duer, RN, MBA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling, Medication Guide
Drug Name:	CAMBIA (diclofenac potassium for oral solution)
Application Type/Number:	NDA 22-165
Applicant/sponsor:	Kowa Pharmaceuticals America, Inc.
OSE RCM #:	2008-1622

1 INTRODUCTION

On September 27, 2007 the Agency received a new drug application (NDA) for diclofenac potassium powder sachet for oral solution for the treatment of acute migraine attacks with or without aura in adults. The original submission was from ProEthic, but as of September 1, 2008, ProEthic changed its name to Kowa Pharmaceuticals America, Inc. and assumed responsibility for all sales and marketing functions operating in the U.S. On October 27, 2008 the Agency issued a complete response letter for this NDA. On December 12, 2008, Kowa Pharmaceuticals America, Inc. submitted a complete response to the October 27, 2008 action letter.

On October 7, 2008, the Division of Neurological Products (DNP) requested that the Division of Risk Management (DRISK) review the proposed CAMBIA patient labeling. On April 17, 2009 an internal labeling meeting was held by DNP so the review team could come to consensus on the proposed professional labeling for CAMBIA. At that meeting DNP requested that DRISK refer to the approved Medication Guide (MG) for NDA 21-926 (Treximet Tablets) dated April 15, 2008 and the Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) dated April 19, 2007 as comparators for the review of the CAMBIA MG.

2 MATERIALS REVIEWED

- CAMBIA Medication Guide (MG) DNP version dated April 17, 2009
- CAMBIA Prescribing Information (PI) DNP version dated April 17, 2009
- Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) dated April 19, 2007
- Approved MG and PI for NDA 21-926 (Treximet Tablets) dated April 15, 2008

3 DISCUSSION

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 submitted by the Applicant and revised by DSPTP has a Flesch Kinkaid grade level of 8.7, and a Flesch Reading Ease score of 54%. 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 7.7 and a Flesch Reading Ease score of 61.5%.

In our current review of the MG we

- simplified the wording and clarified concepts where possible
- ensured that the MG is consistent with the CAMBIA PI, Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Treximet MG

- 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 recommend reformatting 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 CONCLUSIONS AND RECOMMENDATIONS

- We added a standard recommended introductory paragraph in patient information.
- We added section headers consistent with 21CFR 208, including "What is CAMBIA?" and "Before you take CAMBIA, tell your healthcare provider about all your medical conditions".
- We added a section header consistent with the Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), "What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?" However, retaining this information is not consistent with Treximet's MG. We defer to DNP for whether or not to retain this information in the CAMBIA MG.
- In the "How should I take CAMBIA?" section we deleted the storage statement and moved it to the Storage section of the MG.
- In the "Before you take CAMBIA…?" section, we expanded the pregnancy statement and defer to DNP to revise if necessary based on feedback from the MCH team.
- In the "What are the possible side effects of CAMBIA? section, we note that both the NSAID MG and Treximet MG list "Other side effects" in this section, but only common side effects should be listed after the serious side effects. For CAMBIA, nausea and dizziness are the only two adverse events listed as common. Many other side effects were listed in the Clinical Studies section of the CAMBIA PI, but it is unclear what percent cut-off was used, so DNP should revise as appropriate.

- In the “Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) section we note that this information is consistent with the NSAIDs MG, but retaining this information is not consistent with Treximet’s MG. We defer to DNP for whether or not to retain this information in the CAMBIA MG. If this information is not retained, the required statements located at the end of the CAMBIA MG should appear after the “What are the ingredients in CAMBIA” section.

Please let us know if you have any questions.

13 pages withheld after this page as B4 (draft labeling)

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

/s/

Robin E Duer
5/13/2009 12:12:06 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
5/13/2009 12:57:14 PM
DRUG SAFETY OFFICE REVIEWER