CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-165

<u>OTHER ACTION LETTERS</u>

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-165

COMPLETE RESPONSE

ProEthic Pharmaceuticals, Inc.
Attention: John M. Ostrander, PD, PhD
Sr. Director Regulatory Affairs
530 Industrial Park Blvd.
Montgomery, AL 36117

Dear Dr. Ostrander:

Please refer to your new drug application (NDA) dated September 27, 2007, received September 27, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for diclofenac potassium for oral solution for the treatment of acute migraine attacks with or without aura in adults.

We acknowledge receipt of your amendments dated October 30, 2007, (2) March 18, May 6, and July 21, 2008.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. Before this application may be approved, you must address the following:

1. You have not provided sufficient information to allow us to write adequate product labeling for diclofenac potassium for oral solution. Although we acknowledge that you have conducted a search of the published literature, you have limited your search to the years 2004-2007. We are aware of additional published studies that provide information on the potential for diclofenac to induce developmental toxicity (cf. Carp H et al. *Eur J Obstet Gynecol Reprod Biol* 28(3):273-277, 1988; Foerster M et al. *Teratology* 50(5):34A, 1994; Ragbetli MC et al. *Brain Res* 1174:130-135, 2007; Korkmaz A et al. *Turkish J Med Sci* 24(1):27-31, 1995). At least one of these studies was published in 2007, but was not included in your reference list.

(b) (4)

Therefore, you need to conduct a comprehensive search of the published scientific literature to identify studies that provide data that may impact the nonclinical sections of labeling. In order to facilitate the review process, copies of all relevant articles should be provided.

2. We have included draft labeling with this letter. However, in addition to those places in this draft labeling where we have indicated that additional language may be necessary, our review of the literature search we have requested above may necessitate additional labeling changes. Further, as discussed below, you must submit a Medication Guide as part of a REMS. We have included a draft Medication Guide, but we are continuing to perform a detailed review of that document. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

3. You must submit a proposed REMS, as described below. We note that, on October 6, 2008, you submitted a draft Medication Guide via electronic communication. Please submit this Medication Guide to your NDA 22-165 as part of your response to this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA has determined that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for diclofenac potassium for oral solution to ensure that the benefits of the drug outweigh the risks. Nonsteroidal 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.

Your proposed REMS must contain the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. The draft Medication Guide should be provided as a formal submission to the NDA. Pursuant to 21 CFR Part 208, FDA has determined that diclofenac potassium for oral solution 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 diclofenac potassium for oral solution. FDA has determined that diclofenac potassium for oral solution 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 diclofenac potassium for oral solution. Under 21 CFR Part 208 and in accordance with 505-1, you are

responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed diclofenac potassium for oral solution.

Timetable for Assessment: The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than by 18 months and 3 years, and in the 7th year after the REMS is initially approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the assessment interval.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include an evaluation of:

a. Patients' understanding of the serious risks of 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

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

We note that you proposed the Trade Name "Cambia" in a July 22, 2008 amendment to the NDA. The proposed Trade Name is under review.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call James H. Reese, Ph.D., RAC, Regulatory Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: REMS Template
REMS Supporting Document Template
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/

Russell Katz
10/27/2008 06:47:28 PM