DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-926/S-012/S-011

SUPPLEMENT APPROVAL

FULFILLMENT OF POSTMARKETING REQUIREMENTS

NEW POSTMARKETING REQUIREMENTS

Pernix Therapeutics
Attention: Leslie Sands, MS, RAC
10 North Park Place, Suite 201
Morristown, NJ 07960

Dear Ms. Sands:

Please refer to your supplemental New Drug Application (sNDA) dated and received November 14, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Treximet (sumatriptan/naproxen)10mg/60mg.

We acknowledge receipt of your amendments dated the following:

December 19, 2014	March 6, 2015	March 25, 2015	April 24, 2015	May 8, 2015
February 13, 2015	March 19, 2015 (2)	April 16, 2015	May 6, 2015	
February 24, 2015	March 24, 2015	April 23, 2015	May 7, 2015	

This Prior Approval supplemental new drug application proposes sumatriptan/naproxen for the acute treatment of migraine with or without aura in adolescents 12 to 17 years old.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

Additionally, we note that the Prior Approval labeling supplement (S-011) dated April 22, 2014 proposed labeling in Physician Labeling Rule (PLR) format. This labeling was incorporated into our review of this supplemental application.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to carton and immediate-container labels submitted on March 19, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-926/S-012**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Lana Chen
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4352
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We refer to the deferred pediatric studies noted in our original approval letter dated April 15, 2008:

1277-1 Conduct a controlled effectiveness study of Treximet for the acute treatment of migraine attacks with or without aura in pediatric patients ages 12 years to 17 years.

1277-2 Conduct a long-term open label safety study in pediatric patients with migraine ages 12 years to 17 years.

We have reviewed your supplemental application and conclude that the above requirements were fulfilled.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We have waived the pediatric requirement for ages 0 months to up to 6 years because necessary studies are impossible or highly impracticable in that age group.

In our April 15, 2008, approval letter, we stated that pediatric studies in children ages 6 years to up to 11 years should be deferred until additional safety and effectiveness data have been collected in older children and we make a determination as to whether pediatric studies are practicable for children ages 6 years to 11 years. You have submitted safety and efficacy data of Treximet for the treatment of migraine in in children ages 12 years to 17 years. Based on our review of these data, and of other information, we have determined that pediatric studies to evaluate the safety and efficacy of Treximet in children ages 6 years to 11 years with migraine are practicable and will be required, as described below.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must

be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2910-1 Conduct a juvenile rat toxicology study to identify the unexpected serious risk of adverse effects of sumatriptan/naproxen on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study must evaluate effects of sumatriptan/naproxen on growth, reproductive development, and neurological and neurobehavioral development.

Final Protocol Submission: November 2016
Study Completion: November 2017
Final Report Submission: May 2018

2910-2 Conduct a pharmacokinetics (PK) study in children ages ≥6 years to 11 years with migraine. Using information from this PK study, conduct a controlled efficacy study in children ages ≥6 years to 11 years with migraine. Conduct a long-term open-label safety study in pediatric patients with migraine ages ≥6 years to 11 years. The long-term safety study must provide a descriptive analysis of safety data in at least 50 pediatric patients treated with Treximet for a duration of at least 6 months, treating on average at least one migraine attack per month, at doses evaluated in the efficacy study.

Final Protocol Submission: November 2016
Study Completion: November 2020
Final Report Submission: May 2021

Submit the protocol(s) to your IND 68,436, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research

Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266
You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ERIC P BASTINGS
05/14/2015