DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-926 **NDA APPROVAL**

POZEN, Inc.
Attention: Paul A. Ossi
Sr. Vice President, Regulatory Affairs
1414 Raleigh Road, Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your new drug application (NDA) dated August 5, 2005, received August 8, 2005, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Treximet™ (sumatriptan and naproxen sodium) Tablets. Each tablet contains sumatriptan (85 mg as the succinate) and naproxen sodium (500 mg).

We acknowledge receipt of your submissions dated October 11, 2007, January 11, 2008, January 14, 2008, and April 7, 2008.

Your October 11, 2007 submission constituted a complete response to our June 8, 2006 action letter.

This new drug application provides for the use of Treximet™ (sumatriptan and naproxen sodium) Tablets for the acute treatment of migraine attacks with or without aura in adults.

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

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 are waiving 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 addition, we are deferring submission of your pediatric studies for ages 6 years to 17 years because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The findings in adults, and on which the current approval is based, demonstrate sufficient safety to proceed with pediatric studies in children ages 12 years to 17 years. Pediatric studies in children ages 6 years to up to 11 years should be delayed until additional safety and effectiveness data have been collected in older children and we make a determination whether pediatric studies are practicable for children ages 6 years to 11 years.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required pediatric postmarketing studies. The status of this required pediatric postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This requirement is listed below.

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.

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

Final Report Submission:	Within 3 years of the date of approval

As noted above, we will determine if you must perform studies in pediatric patients ages 6 years to 11 years after we have reviewed the above required studies.

Submit final reports to this NDA 21-926. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

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 holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct a postmarketing clinical trial to assess the known serious risk of hypertension associated with exposure to sumatriptan succinate and naproxen sodium. We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of hypertension. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess the known serious risk of hypertension. Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk. Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial:

3. A randomized, double-blind, active comparator clinical trial of Treximet™ in adults with episodic migraine dosed with either Treximet™, naproxen sodium 500 mg, or sumatriptan 85 mg

to further assess the hypertensive effects of Treximet™ relative to each of its two active ingredients. The timetable you have submitted states that you will conduct this clinical trial according to the following schedule:

Final Report Submission: Within 24 months of the date of approval

Submit protocols to your IND 68,436, with a cross-reference letter to this new drug application (NDA) 21-926. Submit final reports to your NDA 21-926. Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

You are required to report periodically to FDA on the status of this clinical trial pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or trial otherwise undertaken to investigate a safety issue associated with Treximet™.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENT

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(2)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of 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 Treximet™ 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 Treximet™. FDA has determined that Treximet™ 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 Treximet™. Nonsteroidal anti-inflammatory drugs, including naproxen sodium, are associated with numerous safety risks, including an increased risk of cardiovascular events and gastrointestinal toxicity. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Treximet™.

Your proposed REMS, submitted on April 15, 2008 in an electronic communication, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your April 15, 2008 submission. The timetable you submitted is as follows:

1st FDAAA assessment: November 2009 (18 months from approval)
2nd FDAAA assessment: May 2011 (3 years from approval)
3rd FDAAA assessment: May 2015 (7 years from approval)

Information needed for assessment of the REMS should include but may not be limited to:

a. Survey of patients' understanding of the serious risks of Treximet™
b. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-926."

CARTON AND IMMEDIATE CONTAINER LABELS

Please submit final printed carton and container labels that are identical to your January 14, 2008 carton and container labels, and also include the minor editorial revisions indicated below, as soon as they are available, but no more than 30 days after they are printed.

On April 15, 2008, we note that you agreed to the following revisions to the Treximet carton and container labels submitted on January 14, 2008:

General Comments:

1. Relocate the dosage form statement so that it is to the right of and adjacent to the established name or, alternatively, relocate the statement of strength so that it is below the dosage form statement (see examples below).

Treximet (sumitriptan and naproxen sodium) Tablets 85 mg/500 mg

2. Increase the size and prominence of the statement of strength.
3. Remove the "New" callout from the labels and labeling.

Container Labels - Sides, Top, and Bottom

1. See General Comment #1 above.
2. Delete the wording [redacted]
3. Add the drug administration precautionary statement "Tablets should not be split, crushed, or chewed" or similar verbiage.

Carton Labeling - Outside

1. Add the drug administration precautionary statement "Tablets should not be split, crushed, or chewed" or similar verbiage.
2. Add the wording "Provide a Medication Guide to each patient to whom this drug product is dispensed" or similar verbiage.

Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005). 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." 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.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

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 Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

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