

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-926

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-926

NAME OF APPLICANT / NDA HOLDER

POZEN Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

TREXIMA

ACTIVE INGREDIENT(S)

sumatriptan succinate and naproxen sodium

STRENGTH(S)

sumatriptan 85 mg (as the succinate) and naproxen sodium 500 mg

DOSAGE FORM

Tablet (oral)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

4,816,470

b. Issue Date of Patent

3/28/1989

c. Expiration Date of Patent

12/28/2006

d. Name of Patent Owner

Glaxo Group Limited

Address (of Patent Owner)

Glaxo Wellcome House, Berkeley Avenue

City/State

Greenford, England

ZIP Code

UB6 0NN

FAX Number (if available)

919-483-7988

Telephone Number

919-483-6983

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ SmithKline Beecham Corp.

Address (of agent or representative named in 1.e.)

One Franklin Plaza

City/State

Philadelphia, PA

ZIP Code

19101

FAX Number (if available)

919-483-7988

Telephone Number

919-483-6983

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) | Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
migraine

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

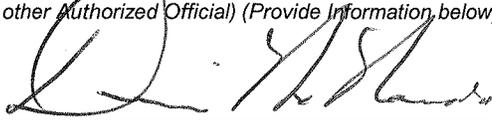
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



7/14/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name POZEN Inc.	
Address 1414 Raleigh Road, Suite 400	City/State Chapel Hill, NC
ZIP Code 27517	Telephone Number 919-913-1030
FAX Number (if available) 919-913-1039	E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

4. Method of Use (continued)	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the proposed labeling for the drug product	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> migraine

Department of Health and Human Services
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1. GENERAL

a. United States Patent Number

5,037,845

b. Issue Date of Patent

8/6/1991

c. Expiration Date of Patent

8/6/2008

d. Name of Patent Owner

Glaxo Group Limited

Address (of Patent Owner)

Glaxo Wellcome House, Berkeley Avenue

City/State

Greenford, Middlesex, England

ZIP Code

UB6 0NN

FAX Number (if available)

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

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No

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2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

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4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Claim 11 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
migrane

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

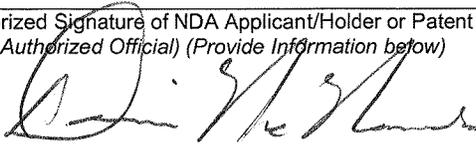
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7/13/05

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<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name POZEN Inc.	
Address 1414 Raleigh Road, Suite 400	City/State Chapel Hill, NC
ZIP Code 27517	Telephone Number 919-913-1030
FAX Number (if available) 919-913-1039	E-Mail Address (if available)

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CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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4. Method of Use (continued)	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 12	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the proposed labeling for the drug product	<i>Use (Submit indication or method of use information as identified specifically in the approved labeling.)</i> migraine

EXCLUSIVITY SUMMARY

NDA # 21-926

SUPPL #

HFD # 120

Trade Name Treximet Tablets

Generic Name sumatriptan and naproxen sodium

Applicant Name Pozen, Inc

Approval Date, If Known: 4/15/08

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 year

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product. –

Question is not applicable for this NDA; NDA provides for a combination product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-204	Aleve (Naproxen Sodium) Tablets
NDA# 18-164	Anaprox (Naproxen Sodium) Tablet
NDA# 20-353	Naprelan (Naproxen Sodium) Controlled Release
NDA# 18-965	Naprosyn (Naproxen Sodium) Suspension
NDA# 21-920	Naproxen Sodium Capsults
NDA# 20-353	Naprelan (Naproxen Sodium) Controlled Release
NDA# 20-080	Imitrex (sumatriptan succinate) Injection
NDA# 20-132	Imitrex (sumatriptan succinate) Tablets
NDA# 20-626	Imitrex (sumatriptan succinate) Nasal Spray

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

MT400-301
MT400-302

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

MT400-301
MT400-302

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 – MT400-301 !

IND # 68,436 YES ! NO
! Explain:

Investigation #2 – MT400-302 !

IND # 68,436 YES ! NO
! Explain:



NDA 21-926

DISCIPLINE REVIEW LETTER

Pozen, Inc.
Attention: Paul Ossi
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your new drug applications (NDAs) submitted on August 8, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trexima (sumatriptan naproxen) tablets.

Our review of the proposed tradename [REDACTED] /Treximet is complete, and we have the following comments:

I. PROPRIETARY NAME REVIEW

- A. DMETS has no objections to the use of the proprietary names, [REDACTED] Treximet. Please note that this is considered a tentative decision and this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names.
- B. DDMAC finds the proprietary names, [REDACTED] Treximet, acceptable from a promotional perspective.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of [REDACTED] we have focused on human factors and safety issues relating to possible medication errors. We have identified the following areas of improvement, which might minimize potential user error.

A. CONTAINER LABEL (9-count)

[REDACTED]

1 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

D. BUSINESS REPLY CARDS

We note that you have submitted additional information in the labeling submission, identified as 'Business Reply Cards'. Since these items are promotional in nature, we recommend that you contact the Division of Drug Marketing, Advertising, and Communication regarding this promotional material.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

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

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/s/

Russell Katz
12/21/2007 06:52:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-926

Pozen, Inc.
Attention: Paul Ossi
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

We acknowledge receipt on October 15, 2007 of your October 11, 2007 resubmission to your new drug application for sumatriptan/naproxen sodium tablets.

We consider this a complete, class 2 response to our August 1, 2007 action letter. Therefore, the user fee goal date is April 15, 2008.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until April 15, 2011. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

NDA 21-926

Page 2

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

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

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/s/

Russell Katz
10/30/2007 01:59:41 PM

Chen, Lana Y

From: Chen, Lana Y
Sent: Monday, September 24, 2007 1:50 PM
To: 'Paul Ossi'
Cc: Chen, Lana Y
Subject: RE: Preliminary Comments for NDA 21-926: September 25, 2007 meeting
Importance: High
Attachments: N 21926 2nd AE End of Review Mtg Prelim Comments.doc

Hi Paul,

Please see attached (in Word) for our preliminary comments, and confirm receipt.

thanks,
Lana

From: Paul Ossi [mailto:POssi@pozen.com]
Sent: Thursday, September 20, 2007 4:53 PM
To: Chen, Lana Y
Subject: NDA 21-926: September 25, 2007 meeting

Hi, Lana. With regard to our meeting scheduled for 9 am on September 25th, one person from our group, [REDACTED] cannot travel from the UK next week and so will participate in the meeting by phone. I am providing below the dial in numbers we wish to use at the meeting so this person can call in. The remainder of our group will meet with you face to face. Please let me know if there is any problem with this. Please also let me know the expected Agency attendees for this meeting. Thanks! See you on Tuesday.

US Dial-in Number: 877-811-8957; International Dial-in Number 706-679-8003

Conference Code: 919 483-5711#

Regards, Paul.

Paul A. Ossi

Senior Vice President, Regulatory Affairs

POZEN Inc.

1414 Raleigh Road

Suite 400

Chapel Hill, NC 27517

9/24/2007

(919) 913-1048 (Direct)

(919) 913-1039 (Fax)

**Appears This Way
On Original**

NDA 21-926
2nd Cycle AE-End of Review Meeting
Preliminary Comments

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 25, 2007 between Pozen and the Division of Neurology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecom). Please note that if there are any major changes to your development plan/the purpose of the meeting/to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager (RPM) to discuss the possibility of including these for discussion at the meeting

Because the key questions you asked can only be answered after review of your response to the approvable letter, and because such a review is beyond the scope of an End Of Review meeting, we believe that no substantive discussion is possible regarding these questions, and that a meeting will not be useful at this time.

Question #1:

Does the Agency concur that these additional preclinical data together with specific responses to comments in the Approvable letter provided herewith are adequate to address the Agency's concerns and that the therapeutic use of NAP/SS does not represent a genotoxic or carcinogenic risk?

Division Response #1:

This question cannot be answered at the present time since a response would require review of all relevant data. You should submit the new information, including final study reports, in a Complete Response to the Approvable Letter.

Question #2:

If the Agency requires data in humans, does the Agency agree that the cytogenetic clinical evaluation with NAP/SS can be considered as a Phase 4 commitment to provide human data for labeling?

Division Response #2:

No. If, upon review of your response, we concur with your position that the apparent synergistic finding is an artifact, then the human cytogenetic study will not be needed. If we do not concur, then the human cytogenetic study will be needed for approval.

Question #2i:

Does the Agency agree with the design presented, and with the definition of a negative outcome for the study?

NDA 21-926
2nd Cycle AE-End of Review Meeting
Preliminary Comments

Division Response #2i:

The proposed design appears to be adequate with the exception that the drug treatments should be repeated daily for 7-10 days, with blood samples taken pretreatment and 24 and 48 hours after the final treatment. The definition of a negative outcome appears to be adequate.

Question #2ii:

Would a negative outcome for the clinical study serve to fully satisfy the Agency's requirements?

Division Response #2ii:

Yes.

Question #3:

Can the Agency provide an update on the status of the review of the proposed trade name?

Division Response #3

Yes. We expect to issue a letter to you regarding the tradename in the next few weeks.

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/s/

Lana Chen
9/24/2007 02:13:09 PM
CSO

Chen, Lana Y

From: Chen, Lana Y
Sent: Tuesday, August 28, 2007 12:07 PM
To: 'Paul Ossi'
Cc: Chen, Lana Y
Subject: NDA 21-926 MR Granted

Hi Paul,

Your Type A Meeting Request dated August 9, 2007 has been granted. We have tentatively scheduled Tuesday, Sep 25 from 9-10 am EDT. Please let me know if this will work for your group, and whether you intend to have a face-to-face or telecon.

Please send me 10 desk copies of your meeting package at least 14 days prior to the meeting.

Desk copies can be sent directly to me via FedEx, UPS or DHL at the following address:

Lana Chen, RPh, Project Manager
Division of Neurology Products
Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4353
Silver Spring, MD 20993-0002

Please also send me an electronic copy of your meeting package, including your questions, via email if possible.

thanks,
Lana

Lana Y. Chen, R.Ph., CDR-USPHS
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
Phone 301-796-1056
Fax 301-796-9842
Email: lane.chen@fda.hhs.gov

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/s/

Lana Chen
8/28/2007 12:13:12 PM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:

X _____
Eric Bastings, MD
Neurology Team Leader, Division of Neurology Products

DATE
July 17, 2007

IND NO.

NDA NO.
21-926

TYPE OF DOCUMENT
Tradename Review—
Treximet

DATE OF DOCUMENT
July 16, 2007

NAME OF DRUG
(sumatriptan and
naproxen)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
Migraine

DESIRED COMPLETION DATE

NAME OF FIRM: Pozen

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

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| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please note the Sponsor requests review of the (1st choice) tradename with labels and labeling provided. See EDR for labeling. Desk copy with CD ROM provided also. Please note 2nd choice is Treximet (alternate spelling).

SIGNATURE OF REQUESTER
Lana Chen, RPh, Project Manager 301-796-1056

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Eric Bastings
7/19/2007 03:00:23 PM

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:

X _____
Eric Bastings, MD
Neurology Team Leader, Division of Neurology Products

DATE
July 5, 2007

IND NO.

NDA NO.
21-926

TYPE OF DOCUMENT
Tradename Review--

DATE OF DOCUMENT
July 2, 2007

NAME OF DRUG
_____ (sumatriptan and
naproxen)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG:
Migraine

DESIRED COMPLETION DATE

NAME OF FIRM: Pozen

REASON FOR REQUEST

I. GENERAL

- | | | |
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| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
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II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

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III. BIOPHARMACEUTICS

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| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please note the Sponsor requests review of the _____ tradename with labels and labeling provided . See EDR for labeling. Desk copy with CD ROM) provided also.

SIGNATURE OF REQUESTER
Lana Chen, RPh, Project Manager 301-796-1056

METHOD OF DELIVERY (Check one)
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SIGNATURE OF DELIVERER

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/s/

Eric Bastings
7/10/2007 03:03:00 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-926

Pozen, Inc.
Attention: Paul Ossi
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

We acknowledge receipt on February 1, 2007 of your January 31, 2007 resubmission to your new drug application for Trexima (sumatriptan/naproxen) tablets.

We consider this a complete, class 2 response to our June 8, 2006 action letter. Therefore, the user fee goal date is August 1, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until August 1, 2010. We note that you have submitted a Proposed Pediatric Study Request (PPSR) on August 1, 2006 (IND 68,436 SN 058), which is under review. If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

NDA 21-926

Page 2

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

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

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/s/

Russell Katz
3/31/2007 12:40:44 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:
X _____
Eric Bastings, MD
Neurology Team Leader, Division of Neurology Products

DATE March 13, 2007	IND NO.	NDA NO. 21-926	TYPE OF DOCUMENT Resubmission—Full Reponse to AE Ltr	DATE OF DOCUMENT June 15, 2007
------------------------	---------	-------------------	--	-----------------------------------

NAME OF DRUG Trexima (sumatriptan and naproxen)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG: Migraine	DESIRED COMPLETION DATE
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NAME OF FIRM: Pozen

REASON FOR REQUEST

I. GENERAL

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| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
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| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
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II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

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| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Please note the Sponsor requests review of the Trexima tradename with further justification provided. See EDR for labeling (31-Jan-2007 submission). Desk copy provided also.

SIGNATURE OF REQUESTER Lana Chen, RPh, Project Manager 301-796-1056	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
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/s/

Eric Bastings
3/14/2007 10:12:45 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-926

Pozen, Inc.
Attention: Paul Ossi
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

We acknowledge receipt on November 7, 2006 of your November 6, 2006 submission to your new drug application (NDA) for Trexima (sumatriptan/naproxen) tablets.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

1. In the End of Review Meeting July 26, 2006, the Division noted that additional data beyond that presented in the meeting briefing document was required to consider your submission a Full Response. In answer to question 2 from your briefing document, the Division stressed that to support your argument that the incidence of adverse events was similar in the Trexima and sumatriptan development programs, you needed to clearly support the validity of both the data itself and the comparisons being made. The Division stated that the calculation of incidence must take into account the number of exposures to the drug. The Division further noted that to be interpretable, the exposure data would need to address the difference between exposure in long term studies and exposure in single/few-exposure efficacy studies. The Division stressed that the data could not simply be pooled for analysis.

Your submission does not contain sufficient data and analysis to address the above issues. You must present the exposure data from the sumatriptan development program in similar detail to the exposure data from the Trexima development program, and provide analysis of how the sumatriptan exposure can be compared to the Trexima exposure. For example, you must incorporate into exposure calculations and summaries the number of drug doses taken for each subject.

2. The Division stated at the End of Review Meeting that you needed to clearly describe the types of events that were used for calculating adverse events incidence. Your Full Response does not describe in sufficient detail the serious adverse events from the sumatriptan program, or provide sufficient information for the Division to determine if the events were, in fact, serious adverse events. You do not sufficiently discuss how the events are comparable

to the serious cardiac adverse event in the Trexima development program.

You must include additional information about the sumatriptan adverse events, such as whether the events were considered serious adverse events in the original Imitrex NDA (and if the definition of serious adverse event was the same as that used in the Trexima studies), and narratives or case report forms as warranted to support your arguments.

You also present data arguing that the rate of subject withdrawal due to treatment-related adverse events is similar in the Trexima and sumatriptan studies. However, insufficient clinical information is provided describing the nature of the sumatriptan events. You must provide additional information (e.g. narratives, case report forms) for the 54 sumatriptan patients that you note in Table 2.5.5 as withdrawing due to cardiovascular adverse events.

3. The Division stated at the End of Review Meeting that for a Full Response you would need to support the validity of the comparisons being made between the sumatriptan and Trexima data. However, in your submission you do not describe any analyses you conducted to validate the comparisons made between sumatriptan and Trexima data. For example, for studies being compared, you must address specific similarities and differences in the enrolled populations, method of collecting adverse events data, comparability of rates of non-cardiac adverse events, comparability of rates of adverse events among placebo groups, comparability of study protocols, etc.

To enable the Division to review your submission, you must describe in greater detail the methodology by which you derived summary tables from source tables, and source tables from primary datasets. For example, Table 2.5.6 and others include 'treatment related' or 'related' in their titles. You must describe the criteria by which events were judged treatment-related or treatment-unrelated. Both treatment-related and treatment-unrelated data must be presented and discussed.

The following is not a 'Full Response' issue, but has been identified as an issue likely to adversely affect our action on your submission if not sufficiently addressed in your submission.

1. The incidence of cardiac adverse events for Trexima is a major safety concern of the Division in consideration of approval of the Trexima NDA. Your current submission addresses this incidence in part through the data in Table 2.5.1, *Treatment Emergent Cardiac Events Related to Study Drug: Expanded Safety Population by Severity*. The Division is concerned that the data in this table is either incorrect, or if correct, presented in insufficient detail to be interpretable. The table lists cardiac adverse events for Trexima in the NDA period (1,162 subjects) compared to the Full Response population (2,628 subjects). In the submission text, section 2.5.5.2.1, you state "The number of subjects in the Trexima database has more than doubled and the incidence of subjects with at least one report of a drug related cardiac event decreased by almost half from 2.3% (27/1162) in the original NDA to 1.3% (34/2628) in this Full Response (Table 2.5.1)." You give no indication that adverse events were recorded differently in these 2 subject groupings, and in any case the Table clearly presents the data as if it was collected in a similar fashion. The Division finds it unlikely, in

the absence of other unexplained factors, that the number of subjects with at least one report of a drug related cardiac adverse event could be 27/1162 (2.3%) for the subjects in the NDA Safety Database, but only 7/1,466 (0.5%), for the subjects added in the Full Response Expanded Safety Database. Furthermore, the Division finds it unlikely that the fraction of this number due to chest pain or chest discomfort (an issue of particular concern that you must address in your Full Response) would be 22/1,162 (1.9%) of patients in the Expanded Safety Database, but none of 1,466 (0%) of the patients added in the Full Response Expanded Safety Database. This data is so clearly unusual and unexpected that we request that you address possible unknown factors that might have influenced this outcome. The Division is additionally concerned that although you provide inadequate detail about how table 2.5.1 was derived from other summary tables and datasets, these other data sources appear to document other cases of treatment emergent cardiac events related to Trexima in subjects newly described in this submission.

Additional Comments

1. The datasets you submitted do not contain in each row a unique patient identifier. If subjects in different studies described in the dataset have the same 'within-study' patient identifier, you must designate an additional column in the combined dataset that contains a unique patient identifier in the context of the current comparison between Trexima and Sumatriptan development programs.
2. Your analysis of adverse events rates for sumatriptan combined subjects taking 50 mg, 70 mg, and 100 mg sumatriptan (presumably mainly non-RT formulation). Please incorporate in your analysis of adverse events from Trexima and sumatriptan consideration of exposure to different doses of sumatriptan.

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

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

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/s/

Russell Katz
12/8/2006 04:37:37 PM

MEMORANDUM OF MEETING MINUTES: ADDENDUM

Meeting Date: July 26, 2006
Location: White Oak
Application: NDA 21-926
Drug: Trexima (sumatriptan/naproxen)
Sponsor: Pozen
Type of Meeting: End of Review (post AE action) Advice : Nonclinical Issues
Meeting Chair: Russell Katz, MD
Meeting Recorder: Lana Chen, RPh

FDA Attendees

Russell Katz, MD Division Director, Division of Neurology Products
Eric Bastings, MD Neurology Team Leader
Ronald Farkas, MD Medical Reviewer
Lois Freed, PhD Supervisory Pharmacologist
David Hawver, PhD, Pharmacology Reviewer
Maryla Guzewska, PhD, Chemistry Team Leader
Lana Chen, RPh, Project Manager
Jeanine Best, MSN, RN, PNP, Policy Analyst, FDA/CDER/OCD/
Safety Policy and Communication Staff (detail)

Sponsor Attendees

POZEN

Marshall Reese, PhD, Executive VP, Product Development
Paul Ossi, Sr. VP, Regulatory and Project Management
Susan Spruill, MS, Sr. Director of Statistics
William Kelce, PhD, VP, Preclinical Development

GSK

Pam Barrett, PharmD, VP Clinical Product Management
Michael Gold, MD, VP, Clinical Development
James Murray, VP, Regulatory Affairs
Christopher Stotka, PharmD, Director, Regulatory Affairs
Shshidhar Kori, MD, Director Clinical Development
Shelly Lener, Pharm. D., Sr. Director, Clinical Development

Background

FDA issued an approvable letter date June 8, 2006 which identified issues that must be addressed prior to NDA approval. The Sponsor requested this end of review conference to discuss the issues involved. This addendum addresses the nonclinical issues discussed.

Discussion

Sponsor's Question:

Does the Agency agree with the proposal to repeat the CHO assay and that adequate justification is provided for not needing to conduct the mouse lymphoma assay?

Division's Response:

No. Both a repeat in vitro chromosomal aberration assay in CHO cells and an in vitro mouse lymphoma tk assay are necessary to further assess the relevance of the apparent synergistic effects of sumatriptan and naproxen observed in the CHO assays submitted. Both in vitro assays should test concentrations of sumatriptan and naproxen between those exhibiting minimal or no toxicity and those resulting in substantial cytotoxicity, in the absence and presence of metabolic activation. The in vitro mouse lymphoma tk assay should include colony sizing.

Sponsor's Question:

Does the Agency agree that the results of the repeat CHO assay can be submitted post-approval?

Division's Response:

No. The repeat CHO assay and the in vitro mouse lymphoma tk assay must be submitted prior to approval.

Summary and Action Items

The Sponsor will consider the Division's advice above.

Minutes Preparer:

Lana Chen, R.Ph.
Project Manager, DNP

Chair Concurrence:

Russell Katz, MD
Director, Division of Neurology Products

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/s/

Russell Katz
9/13/2006 04:23:58 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 26, 2006
Location: White Oak
Application: NDA 21-926
Drug: Trexima (Naproxen/Metoclopramide)
Sponsor: Pozen
Type of Meeting: End of Review (post AE action) Advice
Meeting Chair: Russell Katz, MD
Meeting Recorder: Lana Chen, RPh

FDA Attendees

Russell Katz, MD Division Director, Division of Neurology Products
Eric Bastings, MD Neurology Team Leader
Ronald Farkas, MD Medical Reviewer
Lois Freed, PhD Supervisory Pharmacologist
David Hawver, PhD, Pharmacology Reviewer
Maryla Guzewska, PhD, Chemistry Team Leader
Lana Chen, RPh, Project Manager
Jeanine Best, MSN, RN, PNP, Policy Analyst, FDA/CDER/OCD/Safety Policy and Communication Staff (detail)

Sponsor Attendees

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Marshall Reese, PhD, Executive VP, Product Development
Paul Ossi, Sr. VP, Regulatory and Project Management
Susan Spruill, MS, Sr. Director of Statistics
William Kelce, PhD, VP, Preclinical Development

GSK

Pam Barrett, PharmD, VP Clinical Product Management
Michael Gold, MD, VP, Clinical Development
James Murray, VP, Regulatory Affairs
Christopher Stotka, PharmD, Director, Regulatory Affairs
Shshidhar Kori, MD, Director Clinical Development
Shelly Lener, Pharm. D., Sr. Director, Clinical Development

Background

FDA issued an approvable letter date June 8, 2006 which identified issues that must be addressed prior to NDA approval. The Sponsor requested this end of review conference to discuss the issues involved.

Discussion

1. Will the Agency briefly summarize the outcome of the FDA meeting regarding their decision for the applicability of the NSAID class Boxed Warning and Med Guide to the labeling for the combination product?

Response: The Agency will continue to request Class labeling and a MG for NSAID-containing prescription products. Patients are unlikely to receive the intended NSAID safety message with prescription NSAID-containing products unless a MG is dispensed with the product. Consumer Medication Information (CMI), the usual patient information dispensed with prescription products is not regulated by FDA and varies in content depending on vendor. OTC dose/duration is not a valid reason for granting an exemption because dose/duration safety information is unknown. The NSAID Class MG may be expanded for Trexima to include product-specific information.

2. Does the Agency agree that the additional clinical information described in the Briefing Document and planned for submission in the full response to the Approvable letter is the appropriate type and quantity of data to address the Agency's concern about the potential cardiovascular events with the combination product as compared to sumatriptan alone?

Response: The type of clinical information, and general arguments about the safety of Trexima in the Briefing Document are appropriate to present in greater detail in a Full Response to the Agency. However, the information provided in the Briefing Document is insufficient for us to comment on the likelihood of your arguments ultimately being persuasive after Agency review.

In particular, it is unclear to us what type of events were used to calculate the estimated incidence of treatment-related cardiovascular SAEs presented in the briefing document, and if exposure data were used to calculate the incidences (i.e long term safety data provide multiple exposure data, whereas efficacy study typically provide single exposure date; these data can not simply be pooled for analysis).

For your arguments to be persuasive, particularly those based on information from outside the Trexima development program, you must clearly support the validity of both the data itself, and of the comparisons being made. The calculation of incidence must take into account the number of exposures to the drug, and compare relevant adverse events (e.g. treatment emergent acute coronary events occurring within 3 hours of exposure, within 24 hours of exposure, ...).

The data from your acute clinical pharmacology trial have the potential to address the lack of data on the acute effect of Trexima on blood pressure. The lack of data on the chronic effect of Trexima on blood pressure could potentially be addressed in labeling, with a post-marketing requirement to obtain these data in an adequate long-term study.

3. Does the Agency agree that, taken as a whole, the additional clinical data described in this Briefing Document are adequate for a full response to address the Agency's concerns about potential cardiovascular risk with the combination product as compared to sumatriptan or naproxen alone, without the need for additional studies?

Response: As noted in question 2, the additional clinical data described in the Briefing Document has the *potential* to adequately respond to the Agency's concerns about the cardiovascular risk of Trexima, without the need for additional studies. However, until your Full Response is reviewed, we can not exclude the need for data from additional clinical studies.

Summary and Action Items

The Sponsor will consider the Division's advice above.

Minutes Preparer:

Lana Chen, R.Ph.
Project Manager, DNP

Chair Concurrence:

Russell Katz, MD
Director, Division of Neuropharmacological Drug Products

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/s/

Russell Katz
9/6/2006 03:26:27 PM

Chen, Lana Y

From: Chen, Lana Y
Sent: Tuesday, June 27, 2006 10:14 AM
To: 'Paul Ossi'
Cc: Chen, Lana Y
Subject: RE: NDA 21-926 Trexima: MR Granted

Hi Paul,

Your Type A meeting request dated June 16, 2006 has been granted. We have tentatively scheduled Wed, July 26 from 9-10am for this meeting. [Thank you for the notice about Aug 1, but that date doesn't work for this group.] Please let me know if 7/26 will work for your group, and whether you intend to have a face-to-face meeting or a telecon.

We would like to receive your meeting package no later than 2 weeks prior to the meeting. Please also submit 8 desk copies directly to me. Desk copies can be sent directly to me via FedEx or UPS to the following address:

Lana Chen, RPh, Project Manager
Division of Neurology Products
Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4353
Silver Spring, MD 20993-0002

Please also send me an electronic copy of your meeting package, including your questions, via email if possible.

thanks,

Lana

Lana Y. Chen, R.Ph., CDR-USPHS
Senior Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
Phone 301-796-1056
Fax 301-796-9842
Email: [lana.chen@fda.hhs.gov](mailto: lana.chen@fda.hhs.gov)

From: Paul Ossi [mailto:POssi@pozen.com]
Sent: Friday, June 23, 2006 3:07 PM
To: Chen, Lana Y
Subject: NDA 21-926 Trexima: meeting request

Lana, I have spoken with Jim Murray at GSK and we have agreed that if it works out for your schedule the end-of-review meeting POZEN and GSK have requested for Trexima can be substituted for a previously

scheduled meeting with Dr. Katz that GSK will forgo on August 1st at 11 am. I believe Jim Murray will communicate GSK's agreement with this separately. Please let me know if this works out. Thanks!

Regards, Paul.

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6/27/2006

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/s/

Lana Chen
6/27/2006 10:53:59 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-926

Supplement #

Efficacy Supplement Type SE-

Trade Name: Trexima
Established Name: sumatriptan/naproxen sodium
Strengths: 85 mg/ 500 mg

Applicant: Pozen
Agent for Applicant: n/a

Date of Application: 8/5/05
Date of Receipt: 8/8/05
Date clock started after UN:
Date of Filing Meeting: 8/12/05
Filing Date: 10/8/05
Action Goal Date (optional): 6/8/06

User Fee Goal Date: 6/8/06

Indication(s) requested: Migraine

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (3) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (4) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 4
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? All

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
 “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: I 60,669 & 68,436
- End-of-Phase 2 Meeting(s)? Date(s) May 6, 2004 NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) April 20, 2005 NO
 If yes, distribute minutes before filing meeting.

Project Management

- Was electronic “Content of Labeling” submitted? YES NO
 If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
 YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
 N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO
N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2/9/06

BACKGROUND:

This is an e-NDA in CTD format for Trexima (sumatriptan 85 mg and naproxen 500 mg) . Both sumatriptan and naproxen tablets are previously approved and marketed products.

ATTENDEES: Katz, Russell; Bastings, Eric; Farkas, Ronald; Freed, Lois M; Hawver, David; Heimann, Martha; Oliver, Thomas; Uppoor, Ramana; Yasuda, Sally; Jin, Kun; Chen, Lana

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Team Leader/Reviewer</u>
Medical:	Bastings/ Farkas
Statistical:	Jin/He
Pharmacology:	Freed/Hawver
Statistical Pharmacology:	N/A
Chemistry:	Heimann/Tele
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Uppoor/Yasuda
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Khin/Samuels
Regulatory Project Management:	Chen
Other Consults:	DDMAC/DMETS/DSRCS

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. inspection needed? YES NO

PHARMACOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP inspection needed?			YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?			YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
• Microbiology			YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):
see 10/19/05 74D Filing Letter

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Lana Chen, RPh
Regulatory Project Manager, HFD-120

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (3) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (4) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (5) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (6) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

NDA 20-132 Imitrex (sumatriptan) tablets

NDA 18-164 Anaprox (naproxen) tablets

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a new combination/formulation of sumatriptan 85 mg and naproxen 500 mg

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(j)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
YES NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 60,669 and IND 68,436 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

3. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

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/s/

Lana Chen
5/25/2006 02:47:19 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-926

DISCIPLINE REVIEW LETTER

Pozen, Inc.
Attention: Paul Ossi
1414 Raleigh Road
Suite 400
Chapel Hill, NC 27517

Dear Mr. Ossi:

Please refer to your August 5, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trexima (sumatriptan and naproxen) tablets.

After a preliminary review of the Clinical section of your submission, we have identified the following issues:

FDA has requested that sponsors of all non-steroidal anti-inflammatory containing drugs (NSAID) make labeling changes to their products. All sponsors of marketed prescription NSAIDs, including all prescription naproxen-containing products, have been asked to include a boxed warning, highlighting the potential for increased risk of cardiovascular events and the well described, serious, potential life-threatening gastrointestinal bleeding associated with their use. A medication guide has also been requested for the entire class of prescription products. The degree of NSAID exposure from Trexima justifies including Trexima in this request. We therefore request that you revise the Trexima label and draft a medication guide following the recommendations posted for prescription NSAID products (6/15/2005) at <http://www.fda.gov/cder/drug/infopage/COX2/default.htm#NSAIDletters>.

Medication Guides supersede other patient labeling for a product, so the required NSAID class Medication Guide will replace the proposed PPI for Trexima. You may expand the required NSAID Class Medication Guide to include product specific information.

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

Sincerely,

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

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/s/

Russell Katz
5/9/2006 10:49:13 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 3/30/06

TO: Lana Chen, R.Ph., Regulatory Project Manager
Ronald Farkas, M.D., Clinical Reviewer
Division of Neurological Products, HFD-120

THROUGH: Constance Lewin, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-926

APPLICANT: Pozen, Inc.

DRUG: Trexima

THERAPEUTIC CLASSIFICATION: 4, Standard Review

INDICATION: Treatment of migraine headaches

CONSULTATION REQUEST DATE: October 19, 2005

DIVISION ACTION GOAL DATE: 6/8/06

PDUFA DATE: 6/8/06

I. BACKGROUND:

Trexima is a combination of sumatriptan 85 mg and naproxen sodium 500 mg. This drug was studied in protocols MT400-301 and MT400-302 to determine whether the combination of sumatriptan 85 mg and naproxen sodium 500 mg is superior to placebo, as well as each of the individual components, in the acute treatment of migraine headaches. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. Two sites with high percentage of treatment responders, based on the primary efficacy measure, covering two pivotal studies were selected for inspection. The following protocols were audited: MT400-301 & MT400-302 both entitled "A Double-Blind Multicenter, Randomized, Placebo-Controlled Single Dose Study To Evaluate The Safety And Efficacy Of TreximaTM In The Acute Treatment Of Migraine Headaches."

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol	Insp. Date	EIR Received Date	Final Classification
Norman A. Garrison, M.D./342	Montgomery, AL	MT400-301	Jan. 17-18, 2006	Jan. 27, 2006	VAI
Timothy W. Powell, M.D./364	Spokane, WA	MT400-302	Dec. 12-16, 2005	Feb. 14, 2006	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable.

A. Protocol # MT400-301

1. Norman A. Garrison, M.D. (site # 342)
Drug Research and Analysis Corporation
1758 Park Place, Suite 200
Montgomery, AL 36106

a. What was inspected: Dr. Garrison enrolled 41 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for 40 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No major deviations from FDA regulations were observed. Form FDA 483, Inspectional Observations, was not issued. The protocol requires that subjects be instructed to not take the study medication until they have been notified by the investigator (or designee) that the laboratory results have been reviewed and that the subject has been deemed eligible to participate in the study. It was noted that seven subjects (#s 5257, 5229, 5074, 4260, 3490, 3489, & 3487) reported headaches and recorded study drug administration prior to the clinical investigator's review of the laboratory reports.

d. Data from this site are acceptable.

B. Protocol # MT400-302

1. Timothy W. Powell, M.D. (site # 364)
Rockwood Research Department
400 East Fifth Avenue
Spokane, WA 99202

a. What was inspected: Dr. Powell enrolled 26 subjects. The inspection encompassed an audit of 21 subjects' records. Primary endpoint efficacy data for these 21 subjects were verified.

b. Limitations of inspection: none

c. General observations/commentary: At the completion of the inspection, a Form FDA 483, Inspectional Observations, was issued to Dr. Powell for observations pertaining to protocol violations (subject # 6269 has a history multiple sclerosis and should have been excluded from the study) and inadequate drug accountability (subject #s 6271 and 7786 did not return their study medications per the clinical trials inventory log, but the study records and the case report forms documented that these medications were

returned). A letter dated January 23, 2006, from Dr. Powell in response to the 483 items mentioned that the study medications were not returned.

d. Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, protocol violations and drug accountability issues were reported at Dr. Powell's site, and seven subjects at Dr. Garrison's sites received study drug prior to his review of laboratory reports. However, these deviations do not affect the overall integrity of the data. Data from these two clinical investigators are acceptable in support of NDA 21-926.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.
Consumer Safety Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Sherbert Samuels
4/4/2006 10:26:10 AM
CSO

Constance Lewin
4/4/2006 10:59:58 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: ODS/DSRCS (Room 15B-08, PKLN Bldg.)

FROM:

X _____
Eric Bastings, MD,
Neurology Team Leader, Division of Neurology Products

DATE
February 13, 2006

IND NO.

NDA NO.
21-926

TYPE OF DOCUMENT
PPI/PI

DATE OF DOCUMENT
August 5, 2006

NAME OF DRUG
Trexima
(sumatriptan and naproxen)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
Migraine

DESIRED COMPLETION DATE
May 5, 2006

NAME OF FIRM: Pozen

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: See EDR for labeling (2005-08-05 submission)

SIGNATURE OF REQUESTER
Lana Chen, RPh, Project Manager 301-796-1056

METHOD OF DELIVERY (Check one)
 MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Eric Bastings
2/13/2006 01:52:37 PM

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:
X _____
Eric Bastings, MD
Neurology Team Leader, DNDP

DATE October 19, 2005	IND NO.	NDA NO. 21-926	TYPE OF DOCUMENT: New NDA: Proposed Proprietary Name	DATE OF DOCUMENT August 5, 2005
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NAME OF DRUG Trexima (sumatriptan and naproxen)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG: Migraine	DESIRED COMPLETION DATE 4/1/06
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NAME OF FIRM: Pozen

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
---	--

IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
--	---

V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
NDA 21-926 is available via the EDR at <http://edr/>
Please note that the Trexima tradename was also reviewed under IND 68,436 with our November 2004 request.

SIGNATURE OF REQUESTER Lana Chen, RPh, Project Manager 301-796-1056	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Eric Bastings
10/25/2005 12:50:23 PM