

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-926

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: June 6, 2006

TO: NDA 21-926

FROM: Martha R. Heimann Ph.D.
Pharmaceutical Assessment Lead, ONDQA/DPA-1/Branch 1

SUBJECT: **Overall Compliance and CMC Recommendations:**
NDA 21-926, Trexima (sumatriptan succinate and naproxen sodium) Tablets

The CDER Office of Compliance (OC) issued an overall 'Acceptable' recommendation for NDA 21-926 on June 7, 2006. A copy of the establishment evaluation report is attached. Dr. Chaggan Tele's review for this NDA, dated May 19, 2006, recommends approval of the application, pending an acceptable OC recommendation. Based on Dr. Tele's review, and the Compliance recommendation, the Office of New Drug Quality Assessment recommends approval of NDA 21-926.

**Appears This Way
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07-JUN-2006

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

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Application: NDA 21926/000 Action Goal:
Stamp: 08-AUG-2005 District Goal: 09-APR-2006
Regulatory Due: 08-JUN-2006 Brand Name: TREXIMA
Applicant: POZEN Estab. Name: TABS (SUMATRIPTAN/NAPROXE
1414 RALEIGH RD STE 400 Generic Name: SUMATRITAM/NAPROXEN
CHAPEL HILL, NC 27517
Priority: Dosage Form: (TABLET)
Org Code: 120 Strength: 85 MG/500MG

Application Comment: I AM INTERESTED IN ATTENDING PREAPPROVAL INSPECTION (PAI) OF THE DRUG PRODUCT MANUFACTURING FACILITY. (on 26-AUG-2005 by C. TELE () 301-796-1762)

FDA Contacts: L. CHEN (HFD-120) 301-796-1056 , Project Manager
C. TELE 301-796-1762 , Review Chemist
M. HEIMANN 301-796-1678 , Team Leader

Overall Recommendation: ACCEPTABLE on 07-JUN-2006 by J. D AMBROGIO (HFD-322) 301-827-9049

Establishment: CFN FEI

DMF No: AADA:
Responsibilities:

Profile: CSN OAI Status: NONE

Estab. Comment: OF THE API IN COMBINATION DRUG PRODUCT). (on 26-AUG-2005 by C. TELE () 301-796-1762)

Table with 6 columns: Milestone Name, Date, Type, Insp. Date, Decision & Reason, Creator. Rows include SUBMITTED TO OC and OC RECOMMENDATION.

Establishment: CFN FEI

DMF No: AADA:
Responsibilities:

Profile: TCM OAI Status: NONE

07-JUN-2006

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Establishment Comment: [REDACTED] (on 26-AUG-2005 by C.

TELE () 301-796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC
OC RECOMMENDATION	29-AUG-2005			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN [REDACTED] FEI [REDACTED]

DMF No: [REDACTED]
Responsibilities: [REDACTED] AADA:

Profile: CTL OAI Status: NONE

Establishment Comment: [REDACTED] (on 26-AUG-2005 by C. TELE () 301-796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC
OC RECOMMENDATION	29-AUG-2005			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN [REDACTED] FEI [REDACTED]

DMF No: [REDACTED]
Responsibilities: [REDACTED] AADA:

Profile: TCM OAI Status: NONE

Establishment Comment: [REDACTED] (on 26-AUG-2005 by C.

TELE () 301-796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC
SUBMITTED TO DO	29-AUG-2005	10D			DAMBROGIOJ
DO RECOMMENDATION	07-SEP-2005			ACCEPTABLE BASED ON FILE REVIEW	MSPATARO
GMP INSPECTION COMPLETED 7/27/05, CLASSIFIED NAI					
OC RECOMMENDATION	07-SEP-2005			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

07-JUN-2006

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Establishment: CFN 9610411 FEI 1000291018
GLAXO OPERATIONS UK LTD
PRIORITY STREET
WARE, HERTFORDSHIRE, UK

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER

Profile: CTL OAI Status: NONE

Estab. Comment: RELEASE TESTER OF NAPROXEN DRUG SUBSTANCE MINUS ORGANIC VOLATILE
IMPURITIES. MANUFACTURE OF DRUG PRODUCT, TREXIMA TABLETS. (on 26-AUG-
2005 by C. TELE () 301-796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC
SUBMITTED TO DO	29-AUG-2005	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	30-AUG-2005	GMP			ADAMSS
INSPECTION SCHEDULED	09-MAY-2006		05-JUN-2006		ADAMSS
INSPECTION PERFORMED	05-JUN-2006		05-JUN-2006		ADAMSS
DO RECOMMENDATION	07-JUN-2006			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	07-JUN-2006			BASED ON INVESTIGATOR'S RECOMMENDATION. NO 483 ISSUED. AWAITING EIR. ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Profile: TCM OAI Status: NONE

Estab. Comment: RELEASE TESTER OF NAPROXEN SODIUM DRUG SUBSTANCE MINUS ORGANIC VOLATILE
IMPURITIES. MANUFACTURER OF DRUG PRODUCT, TREXIMA TABLETS. (on 26-AUG-
2005 by C. TELE () 301-796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC
SUBMITTED TO DO	29-AUG-2005	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	30-AUG-2005	GMP			ADAMSS
INSPECTION SCHEDULED	09-MAY-2006		05-JUN-2006		ADAMSS
INSPECTION PERFORMED	05-JUN-2006		05-JUN-2006		ADAMSS
DO RECOMMENDATION	07-JUN-2006			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	07-JUN-2006			BASED ON INVESTIGATOR'S RECOMMENDATION. NO 483 ISSUED. AWAITING EIR. ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: CFN 9611205 FEI 3002807079
GLAXO WELLCOME
2262

07-JUN-2006

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JURONG, , SN

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
Profile: CSN OAI Status: NONE

Estab. Comment: MANUFACTURER AND QUALITY CONTROL OF SUMATRIPTAN SUCCINATE DRUG
SUBSTANCE (ONE OF THE API IN COMBINATION DRUG PRODUCT). (on 26-AUG-2005
by C. TELE () 301-796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC
SUBMITTED TO DO	29-AUG-2005	GMP			DAMBROGIOJ
DO RECOMMENDATION	30-AUG-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	31-AUG-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Profile: CTL OAI Status: NONE

Estab. Comment: MANUFACTURE AND QUALITY CONTROL OF SUMATRIPTAN SUCCINATE DRUG SUBSTANCE
(API IN COMBINATION DRUG PRODUCT). (on 26-AUG-2005 by C. TELE () 301-
796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC
SUBMITTED TO DO	29-AUG-2005	GMP			DAMBROGIOJ
DO RECOMMENDATION	30-AUG-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	31-AUG-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9610421 FEI 3002807078
GLAXO WELLCOME LTD
DL128DT
BARNARD CASTLE, , UK

DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: TESTER OF THE NDA STABILITY BATCHES, STARTING AT THE 18 MONTH TIME
POINT. (on 26-AUG-2005 by C. TELE () 301-796-1762)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-AUG-2005				TELEC

07-JUN-2006

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
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OC RECOMMENDATION

29-AUG-2005

ACCEPTABLE
BASED ON PROFILE

DAMBROGIOJ

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/s/

Martha Heimann
6/8/2006 09:54:48 AM
CHEMIST

NDA 21-926

Trexima™
(sumatriptan succinate/naproxen sodium Tablets)

Pozen® Inc.

Division of Neuropharmacological Drug Products

Chhagan G. Tele, Ph.D.
Division of Pre -Marketing Assessment I
Office of New Drug Quality Assessment

Review of Chemistry, Manufacturing, and Controls



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Chemistry Review Data Sheet

1. NDA 21-926
2. REVIEW #: 1
3. REVIEW DATE: May 19, 2006
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	05-AUG-2005
Amendment (N-000-BC), #006	22-FEB-2006
Amendment (N-000-BC), #008	19-APR-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Pozen Inc.
Address:	1414 Raleigh Road, Suite 400, Chapel Hill, NC 27517
Representative:	Paul Ossi, Senior Vice President, Regulatory and Project Management
Telephone:	(919) 913-1048

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) **Proprietary Name:** Trexima™
- b) **Non-Proprietary Name (USAN):** sumatriptan succinate/naproxen sodium
- c) **Code Name/# (ONDC only):** MT 400
- d) **Chem. Type/Submission Priority (ONDC only):**
 - Chem. Type: 4
 - Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:** 505 (b)(2); The RLD are Imitrex® (sumatriptan succinate) Injection, 12 mg/mL, (GSK NDA 20-080, approved 28-DEC-92 for migraine); Imitrex® Tablets 25

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Chemistry Review Data Sheet

mg, 50 mg, and 100 mg strengths (GSK NDA 20-132, approved 01-JUN-95 for migraine); Imitrex[®] Nasal Spray 5 mg, 10 mg, and 20 mg strengths (GSK NDA 20-626, approved 26-AUG-97 for migraine); and Anaprox[®] (naproxen sodium) Tablets, 275 mg and 550 mg strengths (Roche NDA 18-164, approved 04-SEP-80 for arthritis).

10. PHARMACOL. CATEGORY: For the acute treatment of migraine.
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: Each Tablet contains sumatriptan succinate (85 mg as sumatriptan) and naproxen sodium (500 mg)
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Sumatriptan Succinate

USAN Name (1989): Sumatriptan Succinate

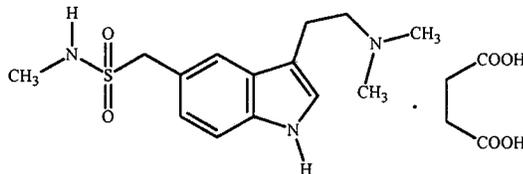
Non-Proprietary Name: 3-[2-(Dimethylamino)ethyl]-*N*-methylindole-5-methanesulfonamide succinate (1:1)

Chemical Formula: $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$

Molecular Weight: 413.49

CAS registry #: 103628-48-4

Structure:



Naproxen Sodium

USAN Name (1973): Naproxen Sodium

Non-Proprietary Name: (-)-Sodium (S)-6-methoxy- α -methyl-2-naphthaleneacetate

CHEMISTRY REVIEW

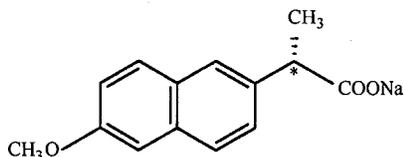
Chemistry Review Data Sheet

Chemical Formula: $C_{14}H_{13}NaO_3$

Molecular Weight: 252.24

CAS registry #: 26159-34-2

Structure:



* Asymmetric carbon center

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (LOA)	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²
[REDACTED]	II	[REDACTED]	[REDACTED]	1	Adequate 16-DEC-05 Dr. Chhagan Tele
	II			1	Adequate 13-MAY-02 Dr. Martha Heimann
	III			4	Adequate per this review
	III			3	Adequate Dr. Alan Schroeder 27-APR-05
	III			4	Adequate per this review
	III			4	Adequate per this review

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

LOA: Letter of Authorization

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,669	Commercial IND (migraine) In Effect 30-AUG-2000
IND	68,436	Commercial IND (migraine) In Effect 18-JAN-2004

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	Pending	
Pharm/Tox	N/A	N/A	
Biopharm	N/A	N/A	
LNC	N/A	N/A	
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	DMETS does not recommend the use of the proprietary name, Trexima. DDMAC finds the proprietary name, Trexima, acceptable from a promotional perspective.	04-APR-06	Laura Pincock, Pharm.D., Safety Evaluator Division of Medication Errors and Technical Support
EA	Acceptable, categorical exclusion granted as per information from Pozen Inc. in this NDA	As per this review	Chhagan G. Tele, Ph.D. (HFD-120)
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-926

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-926 for Trexima™ (sumatriptan succinate/naproxen sodium) Tablets is recommended **APPROVAL** from the CMC standpoint pending on an overall acceptable recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Trexima™ (sumatriptan succinate/naproxen sodium) Tablets is indicated for the acute treatment of migraine. Trexima Tablets are [redacted] immediate release, film coated tablets and are intended for oral administration. Each [redacted] tablet contains 85 mg sumatriptan (as 119 mg sumatriptan succinate) and 500 mg naproxen sodium. This combination product is based on approved drug substances and on the approved single active IMITREX® (sumatriptan succinate) Tablets. A [redacted], film coated, [redacted]-blue, modified capsule-shape tablet was developed to provide the patient with a more convenient presentation for the treatment of migraine. In addition, the excipients have been duplicated from the current IMITREX® Tablet formulation to maintain effective tablet disintegration and dispersion of the sumatriptan component, so that it is less dependent on gastric motility. The formulation uses conventional pharmaceutical ingredients that are well established for use in tablets. Trexima Tablets are a modified capsule-shape, with an

[redacted] They are film coated
 [redacted]-blue and debossed with [redacted] Trexima tablets are packaged into a
 [redacted] compact with desiccant disk (hereafter referred to
 as [redacted]). The [redacted] will contain 9 tablets



Desiccant disk

Executive Summary Section

Conventional pharmaceutical excipients at typical levels are used in Trexima Tablets. The excipient selection was directed by the composition of IMITREX® Tablets and ANAPROX® DS (naproxen sodium 550 mg) Tablets manufactured by Roche Laboratories. Each tablet also contains the inactive ingredients croscarmellose sodium, dextrose monohydrate, dibasic calcium phosphate, FD&C Blue No. 2, lecithin, magnesium stearate, maltodextrin, microcrystalline cellulose, povidone, sodium bicarbonate, sodium carboxymethylcellulose, talc, and titanium dioxide.

_____ is the only non-compendial excipient used in Trexima tablets formulation. The applicant included tests and specifications for _____

/

The drug product will be manufactured, packaged, and controlled by Glaxo Operations UK Limited Ware Hertfordshire. UK site.

/

Stability testing (initial through 12 month time point) on NDA stability batches of Trexima Tablets is conducted at the SmithKline Beecham Corporation, Research Triangle Park, North Carolina. It is indicated by the applicant that the testing of the NDA stability batches, starting at the 18 month time point will be performed at Glaxo Operations UK Ltd, County Durham, UK site.

The specifications for tablets included Description, Identification (HPLC and IR), Assay (HPLC), **Drug -Related Impurities (HPLC)**, **Dissolution (HPLC)**, and Content Uniformity (HPLC). Batch details are provided and batch analysis data are provided for three definitive NDA stability batches of Trexima Tablets, _____

_____ Each of the batches was manufactured according to the proposed commercial process at the proposed commercial site of tablet manufacture and tested by the proposed commercial methods. Validated analytical methods were provided in the submission.

Six months of primary stability data are presented for three batches of Trexima Tablets manufactured on a production-scale at Glaxo Operations, Ware, UK. The batches of Trexima Tablets are identical to those proposed for marketing and were packed in the proposed commercial pack; _____ compact _____ (Batches B916681A, B916682A, and B916683A) and in _____ (Batches B916681P, B916682P, and B916683P) _____

_____ The results of accelerated and long-term stability studies demonstrate the excellent chemical and physical stability of Trexima Tablets when stored for up to 6 months at 25° C/60% Relative Humidity (RH), and for up to 6 months at 40° C/75% RH. No significant changes were observed in description, sumatriptan content, naproxen sodium content, drug-related impurities content, and dissolution, and all results complied with specification. Cosmetic blemishes were observed on some of the Trexima Tablets packaged in the _____ compact _____ after storage for 3 months at 25° C/60% RH and 40° C/75% RH and in the _____ after storage for 6 months at 40° C/75% RH. In addition, data are presented following short-term storage of one of the three batches of Trexima Tablets (B916681) under the stress condition of exposure to light (ICH Q1B option 2). No significant changes were observed in description, sumatriptan content, naproxen sodium content, and drug-related impurities content and all results complied with specification. Eighteen months of supportive stability data are presented for one batch of Trexima Tablets manufactured on a laboratory-scale at GlaxoSmithKline, Research Triangle Park, North Carolina. Tablets were manufactured according to the process described in the original IND 68,436 and were

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Executive Summary Section

The results show no significant changes in description, sumatriptan content, naproxen sodium content, drug-related impurities content, and dissolution after storage for 18 months at 30° C/65% RH and for 6 months at 40°C/75% RH. No significant changes were observed in description, sumatriptan content, naproxen sodium content, or drug-related impurities content after short-term storage under the stress condition of exposure to light (ICH Q1B option 2).

The drug substance, sumatriptan succinate is currently approved for use in GlaxoSmithKline's marketed products Imitrex® Injection and Imitrex® Tablets, and is provided by cross-reference to the parent NDA for this active pharmaceutical ingredient (Imitrex® Injection NDA 20-080, LOA 28-APR-05). Sumatriptan succinate, is currently manufactured and supplied to the applicant by Glaxo Wellcome Manufacturing Pte. Ltd., Jurong, Singapore facility. Manufacture of sumatriptan succinate at the Jurong, Singapore facility was approved in the supplement to NDA 20-080/S-020. Clinical and definitive stability batches of Trexima Tablets were manufactured using sumatriptan succinate sourced from Jurong, Singapore. Sumatriptan succinate is a white to off-white crystalline powder. Naproxen sodium is a USP material and is currently approved for use in various proprietary (ANAPROX® Tablets, Roche NDA 18-164, 04-SEP-80) and over the counter medication (ALEVE). Naproxen sodium is

according to the details Letter of Authorization to access this DMF was provided for cross-reference. The was reviewed and found adequate by Dr. Chhagan Tele, HFD-130 on 16-DEC-05 and found adequate (IR letter sent 03-JAN-06). Naproxen sodium is a white to creamy white, crystalline solid with one chiral center, freely soluble in water at neutral pH. All the batches of Naproxen sodium drug substance presented in the original NDA were

. Batch analysis data of three batches of drug substance used in manufacturing of drug product were provided. Validated analytical methods were provided in the DMF. A retest date of has been established for the bulk Naproxen sodium by on the basis of real time stability data for 3 commercial batches.

B. Description of How the Drug Product is Intended to be Used

Trexima™ (sumatriptan succinate/naproxen sodium) Tablets will be marketed into compact with desiccant disk /9 counts. The maximum recommended total daily dose is sumatriptan (85 mg as sumatriptan-equivalent to 119 mg of sumatriptan succinate) and naproxen sodium (500 mg)/day. Pozen initially provided 6 months of stability data at 25° C/60% RH and 6 months stability data at 40° C/75% RH for registration batches of Trexima tablets. Stability data was updated for 18 months for long term storage in amendment #006 dated 22-FEB-06.

The storage conditions for the drug product were recommended as "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Dispense in

The applicant makes the usual post-approval stability commitments with regards to stability studies indicating that the first three production batches and each container/closure system will continue according to the approved stability protocols through the expiration dating period.

This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR § 25.31(a).

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-926 for Trexima™ tablets is recommended to be granted **Approval** status from CMC standpoint pending on overall acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Chhagan G. Tele, Ph.D.
Branch Chief Name: Ramesh Sood, Ph.D.
Project Manager Name: Lana Chen, Pharm.D.

C. CC Block

See DFS.

114 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

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/s/

Chhagan Tele
5/19/2006 12:45:03 PM
CHEMIST

Ramesh Sood
5/19/2006 01:16:25 PM
CHEMIST