CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22511Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-511

Vimovo

(naproxen and esomeprazole magnesium) delayed release tablets

375 mg/20 mg* and 500 mg/20 mg*

**Each tablet contains 22.3 mg esomeprazole magnesium, equivalent to 20 mg esomeprazole.*

Pozen Inc.

Rajiv Agarwal

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III

CMC REVIEW OF NDA 22-511

For the Division of Gastroenterology Products (HFD-180)

Table of Contents

CMC Review Data Sheet

1. NDA 22-511

2. REVIEW #: 1

3. REVIEW DATE: 07-APR-2010

4. REVIEWER: Rajiv Agarwal

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	30-JUN-2009
Amendment	19-NOV-2009
Amendment	30-NOV-2009
Amendment	04-MAR-2010
Amendment	25-MAR-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Pozen Inc.
Address:	1414 Raleigh Road, Suite 400 Chapel Hill, NC 27517
Representative:	Paul A. Ossi
Telephone:	919-913-1030

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Vimovo
b) Non-Proprietary Name (USAN):	naproxen and esomeprazole magnesium
c) Code Name/# (ONDQA only):	PN 400
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	4
• Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of the signs and symptoms of osteoarthritis, rheumatoid and ankylosing spondylitis in patients at risk for developing NSAID-associated gastric ulcers.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: Each tablet contains naproxen (375 mg or 500 mg) and esomeprazole magnesium (22.3 mg equivalent to 20 mg of esomeprazole)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

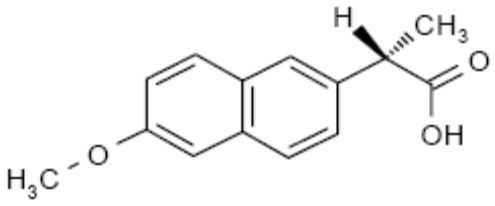
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed0y

__√___Not a SPOTS product

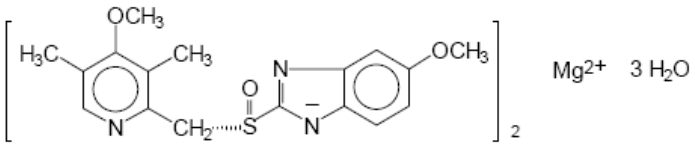
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Naproxen:



Chemical name:	(S)-6-methoxy-α-methyl-2-napthaleneacetic acid
Molecular formula:	$C_{14}H_{14}O_3$
Molecular weight:	230.26

Esomeprazole Magnesium:



Chemical name: bis (5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.\ 3H_2O$
Molecular weight: 767.2 g/mol

RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	20-JUN-2005	Dr. R. D. Costa for ANDA 77-339
	III			3	Adequate	19-DEC-2000	Dr. Donald Klein for DMF Strike Force
	III			3	Adequate	01-AUG-2005	Dr. Craig Bertha for NDA (b) (4)
				3	Adequate	13-SEP-2002	Dr. Prasad Peri for NDA 20-829
	III			3	Adequate	13-JUN-2002	Dr. Jila Boal for NDA 21-400
	III			3	Adequate	20-DEC-2003	Dr. Ramesh Sood for NDA 20-334 (S002)
	III			1	Adequate	24-MAR-2010	Reviewed by Rajiv Agarwal for NDA 22-511.
	III			1	Adequate	24-MAR-2010	Reviewed by Rajiv Agarwal for NDA 22-511.
	III			3	Adequate	o2-AUG-2007	Dr. Craig Berths for NDA 22-152
				1	Adequate	24-MAR-2010	Reviewed by Rajiv Agarwal for NDA 22-511.

(b) (4)			05F92577				
	III		(b) (4)	3	Adequate	9-SEP-2008	Dr. Don Klein for DMF strike force on 9-FEB-2001
	III			3	Adequate	12-MAR-2009	Dr. Bogdan Kurtyka for NDA (b) (4)
				3	Adequate	12-MAR-2009	Dr. Bogdan Kurtyka for NDA (b) (4)
	III			1	Adequate	23-MAR-2010	Reviewed by Rajiv Agarwal for NDA 22-511
				3	Adequate	7-MAR-2008	Dr. Bogdan Kurtyka for NDA 22-262
	III			1	Adequate	24-MAR-2010	Reviewed by Rajiv Agarwal for NDA 22-511
	III			3	Adequate	7-APR-1997	George T. Chen for NDA 19-462 S-19
				1	Adequate	24-MAR-2010	Reviewed by Rajiv Agarwal for NDA 22-511
				3	Adequate	8-NOV-1999	Dr. Don Klein for NDA 20-990
				1	Adequate	24-MAR-2010	Reviewed by Rajiv Agarwal for NDA 22-511

[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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76,301; (b) (4)	
NDA	21-153	Esomeprazole magnesium (**drug substance is also reviewed here**)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	24-MAR-2010	OC
Bio-Pharmaceutics	Adequate*	9-MAR-2010	Tien Mien Chen
Methods Validation	N/A, according to the current ONDQA policy	07-APR-2010	Rajiv Agarwal
EA	Categorical Exclusion granted	22-DEC-2009	Raanan Bloom, OPS

***** It is recommended that the dissolution testing for the naproxen component of the Vimovo tablets, the conventional dissolution methodology for delayed release product, i.e., in the acid stage (pre-exposure) followed by the buffer stage on the same tablet, be performed post approval (amendment dated 4-MAR-2010, refer to Biopharmaceutical review dated 9-MAR-2010).

The CMC Review for NDA 22-511

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The final "Acceptable" recommendation from the Office of Compliance is received on 24-MAR-2010 (Attachment-1).

The labeling information on immediate container and carton labels is adequate.

Therefore, this NDA is recommended for APPROVAL form the CMC perspective.

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

As a Phase 4 commitment, within one year post approval, submit new dissolution data on the testing of naproxen in Vimovo FDC tablets using the Agency's recommended USP dissolution methodology for enteric coated (i.e., delayed release) drug products (refer to Biopharmaceutical review dated 9-MAR-2010). The applicant has committed to the proposal via amendment dated 4-MAR-2010.

II. Summary of CMC Assessments

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

(1) Drug Substance

Information regarding the drug substance, **esomeprazole magnesium** was originally approved in NDA 21-153 for NEXIUM, a Delayed-Release Capsules. This drug substance is manufactured in France. A letter authorizing access to NDA 21-153 is provided.

Similarly, the Chemistry, Manufacturing, and Control information on the **Naproxen** drug substance is provided in the cross referenced DMF (b) (4) from (b) (4). A letter authorizing an access to the DMF is provided in the submission.

(2) Drug Product

PN 400 Tablets have been designed as a single combination tablet of two distinct formulations, an inner enteric coated (delayed release) component of naproxen containing either 375 mg or 500 mg of naproxen and an outer immediate release film coat of esomeprazole magnesium containing 20 mg of esomeprazole (present as 22.3 mg of esomeprazole magnesium). The tablet is designed to release the active ingredients in a coordinated, yet independent, fashion.

Naproxen is an analgesic, while esomeprazole magnesium, a proton pump inhibitor, is included in the formula to reduce gastric acid secretion and subsequently minimize gastric irritation, which can result from naproxen administration.

(b) (4)

Based on the qualitative and quantitative formulation, the two strengths of PN 400 are dose proportional. The 375 mg and 500 mg naproxen core strength is based on a common formulation and hence is proportionally similar in terms of naproxen and all inactive ingredients.

(b) (4)

Esomeprazole magnesium is mixed with other ingredients to form an (b) (4)

(b) (4)

The qualitative and quantitative composition of Phase 1, Phase 3, and primary stability (identical to commercial) batches are summarized in the submission. PN 400 (375 mg/20 mg) batches were not used in any Phase 3 clinical trials. However, one primary stability batch of PN 400 (375 mg/20 mg) was used in a naproxen bioequivalence study, PN 400-105.

This Delayed Release Tablet formulation utilizes conventional pharmaceutical ingredients and manufacturing processes that are well established for use in solid oral dosage forms. PN 400 tablets are packaged into 60 counts HDPE bottles with child resistant cap for commercial use and in 500 counts HDPE bottles and aluminum blisters (10 counts) for hospital use. Both 500 tablets bottles and blisters are not child resistant. Since these packaging configurations are for hospital use, and, therefore, they are exempted from 16 CFR 1700 requirements. Physician samples are available in 6-count HDPE bottles with child resistant cap.

An 24-month of expiration dating period is requested and it is granted based on the submitted stability data.

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

The dosage is one tablet twice daily. The tablets should be swallowed whole with liquid. They should not be split, chewed or crushed. Vimovo should be taken at least 30 minutes before meals.

C. Basis for Approvability or Not-Approval Recommendation

Satisfactory responses to the CMC information requests (claim for categorical exclusion dated 11-APR-2009 and labeling) were received on 19-NOV-2009 and 25-MAR-2010, respectively.

This NDA now is deemed to have provided adequate information on the raw material controls, manufacturing process, specifications for assuring consistent quality of the drug substance and drug product, and container/closure system. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period..

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Rajiv Agarwal, Ph.D; Ph.D

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D, Branch Chief, Branch III, ONDQA

C. CC Block: entered electronically in DARRTS

68 pages withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22511	ORIG-1	POZEN INC	PN 400 NAPROXEN/ESOMEPRAZOLE MAGNESIUM

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

/s/

RAJIV AGARWAL
04/07/2010

MOO JHONG RHEE
04/07/2010
Chief, Branch III