CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-056

CHEMISTRY REVIEW(S)

NDA 22-056

Prilosec® (omeprazole magnesium) for Delayed Release Oral Suspension

AstraZeneca

Maria Ysern, MSc
Review Chemist

Office of New Drug Quality Assessment
Division of Premarketing Assessment II
Branch III

CMC Review of NDA 22-056
For the Division of Gastroenterology Products

Table of Contents

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 22-056

2. REVIEW #:2

3. REVIEW DATE: Feb 27, 2008

4. REVIEWER: Maria Ysern, MSc

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	DEC 20, 2006
Amendment	JUN 27, 2007
Amendment	JUL 03, 2007
Amendment	JUL 11, 2007
Response to teleconference	JUL 25, 2007
BL Amendment	OCT 04, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BL Amendment	Dec 13, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca LP
Address:	1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355
Representative:	George A. Kummeth, Global Director Regulatory Affairs
Telephone:	302-885-8415

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: Prilosec® (omeprazole magnesium) For Delayed Release Oral Suspension
   b) Non-Proprietary Name (USAN): omeprazole magnesium
   c) Code Name/# (ONDQA only): - .
   d) Chem. Type/Submission Priority (ONQA only):
      - Chem. Type: Type 3
      - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Anti-secretory (suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase enzyme)

11. DOSAGE FORM: Sachets of granules and delayed release pellets for oral suspension

12. STRENGTH/POTENCY: 2.5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed

    ___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
    Magnesium bis (5-methoxy-2-{[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl} 1H-benzimidazolide).
    CAS 95382-33-5

Molecular formula: $(C_{17}H_{18}N_3O_3S)_2\,Mg$ MW: 713.1 g/mol (anhydrous)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III			4			
—	II			1	Adequate	April 19, 2006	
—	II			1	Adequate	April 19, 2006	
—	II			1	Adequate	July 31, 2002 Art Shaw, PhD	

b(4)

[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
NDA	21-229	Prilosec(omeprazole magnesium) Delayed Release Tablets
NDA	19-810	Prilosec Delayed Release Capsules

18. SQAATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable Acceptable	Jan 29, 2007 Aug 07, 007	Shirnette Ferguson
Pharm/Tox	n/a		
Biopharm	n/a		
Methods Validation	Will validate per ONDQA policy		
DEMETS	Label change recommended. (increase in prominence of the (omeprazole) term	April 17, 2007	Kristina C. Arnwine, PharmD, Safety Evaluator
EA	Finding of No Significant Impact	Feb 26, 2007	Raanan A. Bloom, Ph.D.
Microbiology	n/a		

19. ORDER OF REVIEW : N/A

The Chemistry Review # 2 for NDA 22-056

The Executive Summary

NDA 22-056 for Prilosec® (omeprazole magnesium) For Delayed Release Oral Suspension was "Approvable" on October 19, 2007 due to labeling and other clinical issues

A labeling (BL) amendment was submitted by the applicant on Dec 13, 2007. The information provided was reviewed and found satisfactory.

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the information provided in this NDA and BL amendment dated Dec 13, 2007, from the standpoint of chemistry, manufacturing and controls, this NDA can be approved.

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

n/a.

A. Labeling & Package Insert:

The applicant submitted a BL Amendment Dec 13, 2007 which included some changes, per our recommendations, to the carton/container labels as described below:

1. Immediate Container Labels:

The company has agreed to increase the size and prominence of the established name to insure that it is ½ the size of the proprietary name. and to change the established name from "omeprazole" to "Omeprazole magnesium".

In the BL amendment Dec 13, 2007 the corrections were included, and are adequate. An example of the changes is included below:

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry-*__1__

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/s/

Maria Ysern
2/28/2008 07:59:49 AM
CHEMIST
CMC Review #2

Moo-Jhong Rhee
2/28/2008 08:41:32 AM
CHEMIST
Chief, Branch III

NDA 22-056

Prilosec® (omeprazole magnesium) for Delayed Release Oral Suspension

AstraZeneca

Maria Ysern, MSc
Review Chemist

Office of New Drug Quality Assessment
Division of Premarketing Assessment II
Branch III

CMC Review of NDA 22-056
For the Division of Gastroenterology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-056

2. REVIEW #: 1

3. REVIEW DATE: October 15, 2007

4. REVIEWER: Maria Ysern, MSc

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	DEC 20, 2006
Amendment	JUN 27, 2007
Amendment	JUL 03, 2007
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a) Proprietary Name: Prilosec® (omeprazole magnesium) For Delayed Release Oral Suspension

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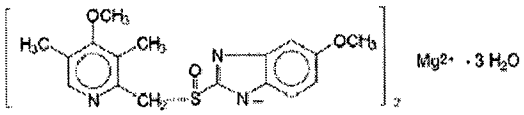
CAS 95382-33-5

Molecular formula: $(C_{17}H_{18}N_3O_3S)_2\,Mg$ MW: 713.1 g/mol (anhydrous)



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b(4)

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[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
NDA	21-229	Prilosec(omeprazole

		magnesium) Delayed Release Tablets
NDA	19-810	Prilosec Delayed Release Capsules

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable Acceptable	Jan 29, 2007 Aug 07, 007	Shirnette Ferguson
Pharm/Tox	n/a		
Biopharm	n/a		
Methods Validation	Will validate per ONDQA policy		
DEMETS	Label change recommended. (increase in prominence of the (omeprazole) term	April 17, 2007	Kristina C. Arnwine, PharmD, Safety Evaluator
EA	Finding of No Significant Impact	Feb 26, 2007	Raanan A. Bloom, Ph.D.
Microbiology	n/a		

19. ORDER OF REVIEW : N/A

The Chemistry Review for NDA 22-056

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the information provided in this NDA, from the standpoint of chemistry, manufacturing and controls, this NDA can be approved pending resolution of some minor labeling issues.

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

n/a.

II. Summary of Chemistry Assessments

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

(1) Drug Substance:

All information regarding the drug substance, omeprazole magnesium, is provided in the approved NDA 21-229 and all the supplements thereto. (NDA 21-229 was submitted on Jan 27, 2000 and approved on Jun 30, 2003. It provides for the treatment of frequent heartburn, two or more days a week, for consumers 18 years and older).

(2) Drug Product:

Prilosec for Delayed-Release Oral Suspension, which is termed as "Prilosec Sachets" in this submission, consists of omeprazole pellets and excipient granules filled into single use aluminum sachets.

The omeprazole pellets are described in Prilosec OTC NDA 21-229 and contain the active omeprazole magnesium and the following excipients: glyceryl monoestearate — , Hydroxpropyl cellulose, hydroxypropylmethylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate ——— sugar spheres ——— talc, triethylcitrate and —

b(4)

Omeprazole pellets rapidly sediment in water and the excipient granules will help maintain the omeprazole pellets in suspension.

The excipient granules are composed of: hydroxypropyl cellulose [redacted] b(4)

[redacted] Xantan gum [redacted]

[redacted] The citric acid [redacted]

[redacted] iron oxide [redacted]

[redacted] The function of the excipient granules is to make the reconstituted suspended product viscous and [redacted] to keep the omeprazole pellets dispersed and the enteric coating intact prior to administration.
The same excipients and omeprazole pellets, in different quantities, are used for the 2.5 mg and 10 mg strengths.

The container closure consists of a sachet [redacted] b(4)

[redacted] which is in contact with the drug product. The filled sachets are packed in a carton.
Stability data have been provided in Amendment dated June 27, 2007, that support the 30 month expiry date.

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

Prilosec for Delayed-Release Oral Suspension should be administered as follows:

- Empty the contents of a 2.5 mg packet into a container containing 5 mL of water or
- Empty the contents of a 10 mg packet into a container containing 15 mL of water.
- Stir
- Leave 2 to 3 minutes to thicken.
- Stir and drink within 30 minutes.
- If any material remains after drinking, add more water, stir and drink immediately.

C. Basis for Approvability or Not-Approval Recommendation

The information on the manufacturing of the drug substance has been provided by cross reference to NDA 21-229 OTC, approved on Jun 30, 2003.
The manufacturing of Prilosec (omeprazole magnesium) for Delayed Release Oral Suspension has been described or referenced. The characteristics of the drug product were identified during its development and adequate measures were taken to

improve its quality. Critical quality attributes such as suitable viscosity, acid resistance properties [redacted] contents were properly identified and controlled. b(4)
The characteristics of the excipients are well established and in-process control of excipient granules is maintained by testing of the [redacted]
Fill weights of the omeprazole pellets and the excipient granules are well controlled to ensure accurate filling of the sachets and no leakage of the sealed sachets.
The specification for the drug product, Prilosec sachets has been adequately justified.

The packaging was deemed adequate to protect the product during 30-month shelf life for both strengths.
AstraZeneca has provided an Environmental Assessment for Prilosec® omeprazole magnesium) Delayed Release for Oral suspension (2.5 mg or 10 mg), and after being reviewed by ONDQA, a Finding of No Significant Impact (FONSI) was recommended .

The inspection of the manufacturing sites resulted in an Overall Compliance recommendation of "Acceptable" for all the sites, including the alternative site described in the amendment dated July 25, 2007.
The sponsor has agreed to change the established name from omeprazole to omeprazole magnesium and the size and prominence of the established name has been increased as requested.

Based on the information provided, this NDA is recommended for approval from the standpoint of CMC pending resolution of minor labeling issues in the next review cycle.

III. Administrative

A. Reviewer's Signature in DFS

B. Endorsement Block in DFS

Chemist Name/Date: Maria Ysern, MSc.
Branch Chief/ /Date: Moo-Jhong/Rhee, PhD
Project Manager: Linda Athey.
Clinical Project Manager: Ray Barraco.

C. CC Block in DFS

64 Page(s) Withheld

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____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Maria Ysern
10/17/2007 03:46:00 PM
CHEMIST

Moo-Jhong Rhee
10/17/2007 03:49:08 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

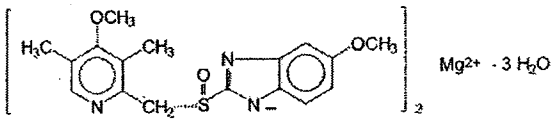
OND Division:	Division of Gastroenterology Products
NDA:	22-056
Applicant:	AstraZeneca
Stamp Date:	12/20/06
Received by PAL:	1/10/07
Review Date:	4/2/07
PDUFA Date:	10/20/07
Trademark:	Prilosec®
Established Name:	omeprazole magnesium
Dosage Form:	Granules
Route of Administration:	oral
Indication:	Proton pump inhibitor
PAL:	Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	☒	
Comments for 74-Day Letter		☒

A. Summary

Prilosec® (omeprazole magnesium) For Delayed-Release Oral Suspension has been submitted in two strengths in the present application, 2.5 and 10 mg. (It is also referred to as Prilosec Sachets throughout the submission.) AstraZeneca has submitted this NDA in fulfillment of their post-marketing commitment to develop an age-appropriate formulation of Prilosec (omeprazole) Capsules (NDA 19-810/S-074) for pediatric patients aged 0 to 2 years. The product, which is packaged in single-use aluminum packets, is suspended in water prior to administration by spoon, drinking, or through enteric tubes. The 2.5 mg strength is suspended in 5 mL of water and the 10 mg strength is suspended in 15 mL.

The active drug substance in this product is the magnesium salt of omeprazole (racemic)



It was originally approved for use in Prilosec Tablets (OTC), NDA 21-229. CMC information regarding the drug substance is not provided in this NDA submission; instead, it is cross-referenced to NDA 21-229.

The product formulation is a mixture of omeprazole delayed release pellets and excipient granules:

- *Omeprazole pellets contain:* omeprazole magnesium, glycerol monostearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polysorbate — sugar spheres, talc, and triethylcitrate. The omeprazole pellets used in this product are the same as the omeprazole enteric coated pellets used in NDA 21-229 in the production of Prilosec

b(4)

b(4)

Delayed-Release Tablets; they are produced in the
All information regarding the omeprazole pellets is cross-referenced to NDA 21-229.

- *Excipient granules contain*: xanthan gum, citric acid, iron oxide and hydroxypropyl cellulose. The identical excipient granule formulation has been approved for use in NDA 21-957, Nexium® (esomeprazole magnesium) For Delayed-Release Oral Suspension. The function of the excipient granules is to make the reconstituted suspended product viscous and thereby retard sedimentation, as well as to make the suspension to keep the enteric-coating on the omeprazole pellets intact prior to administration

b(4)

Manufacture of the product

b(4)

The proposed product specification includes: assay for omeprazole content by HPLC (with acceptance criteria of omeprazole), related compound impurity testing by HPLC with acceptance criteria conforming to ICH guidance (unidentified impurities NMT identified impurities NMT and total impurities NMT , uniformity of dosage units of target fill), and dissolution testing.

b(4)

Table 11 Specification for Prilosec Sachets 2.5 mg and 10 mg

Test procedure	Acceptance criteria	Method reference
Description		
Identification omeprazole		
Identification magnesium		
Assay		
Uniformity of dosage units[a]		
Acid resistance		
Dissolution		
Organic impurities		

b(4)

This proposed specification is the same as the approved specification for Prilosec OTC in NDA 21-229, with the exception of description, uniformity of dosage units, and dissolution, and consequently, only these last two parameters will receive further attention in this assessment (see Critical Issues below). Water content, viscosity, residual solvents / ——,, and pH testing, although shown to be important to the proper functioning of the product, are omitted from the drug product specification because these parameters are adequately controlled in the product by controlling them in the excipient granules (the specification for the excipient granules is as approved in NDA 21-957). b(4)

Nine months of primary stability data (three batches at each strength) determined under ICH conditions (at 25°C and 30°C) and 6 months at accelerated conditions showed no significant changes over the 9 month period. (Testing included evaluation of the reconstituted product during the proposed in-use period of 30 minutes.) Based on these data, the applicant extrapolates to an —— expiration date (with room temperature storage), in accord with ICH Q1E. b(4)

The product name Prilosec® (omeprazole magnesium) for Delayed Release Oral Suspension is in accord with current naming convention, is in line with recently approved comparable PPI products [NEXIUM® (esomeprazole magnesium) for Delayed Release Oral Suspension], and consequently is acceptable.

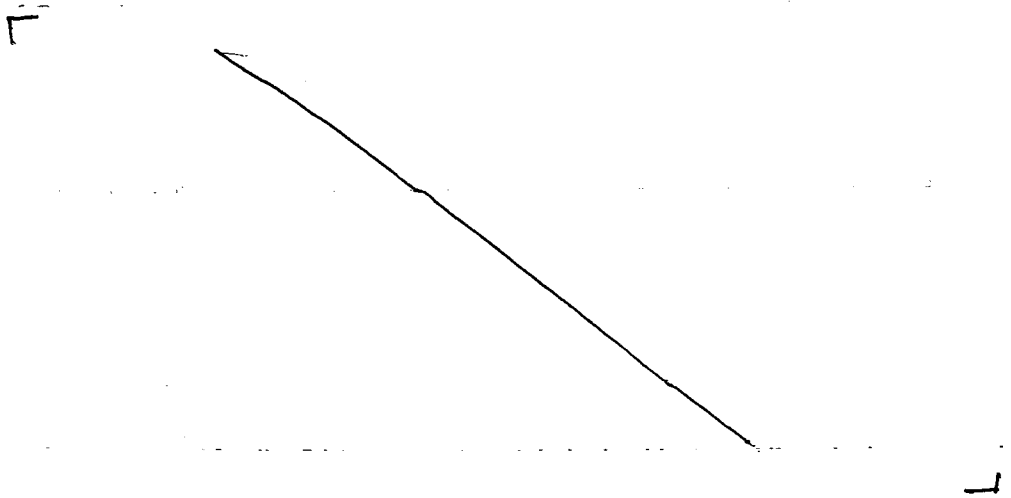
The applicant has submitted an environmental assessment with the application. This has been sent as a consult to OPS for evaluation.

Inspection requests for the two facilities involved in the manufacture of the drug substance and drug product have been entered into EES, as listed in the appended report.

B. Critical issues for review

Astra Zeneca has recently obtained approval for a very similar product, NEXIUM® (esomeprazole magnesium) for Delayed Release Oral Suspension. The current submission closely parallels that submission, with only the following major issues requiring closer scrutiny

- Dissolution:
  For delayed release solid dosage forms, USP requires dual stage dissolution testing, Stage 1 being a two hour dissolution test under acidic conditions, followed by Stage 2 dissolution testing in buffered medium (pH 6.8). The amount of drug dissolved at the end of each stage is measured, and for delayed release products cannot exceed 10% at the end of Stage 1. The applicant proposes to modify this test ——



b(4)

In the present reviewer's opinion, the proposed approach is scientifically sound and acceptable. However, the proposed dissolution limit appears too liberal in view of the batch analysis data which show that the dissolution results for six batches range between This should be more fully evaluated.

b(4)

- Content Uniformity

  The uniformity of dosage will be determined on a weight basis and according to the specification above, it will meet USP requirements. Testing will include sachets in a manufactured drug product batch, while the USP requirement is based on testing 10 or 30 sachets, with the requirement (for 30 sachets) that no individual unit be outside of 75% to 125% of label claim and the relative standard deviation not exceed 7.8%. The applicant has stated that all sachets will be of label claim, but has not identified a limit for the standard deviation. (The standard deviations for six batches have ranged between) It may be necessary to ask the firm to better define the acceptance criterion for the dose uniformity test.

b(4)

- Expiration Dating
  Since the omeprazole pellets and excipient granules are also used in the manufacture of other products at AstraZeneca, it is likely that these will be stored prior to use in the manufacture of this product. It is important to clarify when expiration dating will begin, at the time the pellets and granules are manufactured, or at the time the Prilosec Sachet is manufactured. If the latter is the case, the applicant will need provide data to define maximum holding times and storage conditions for the pellets and granules prior to use in the manufacturing process.

C. Comments for 74-Day Letter -- None

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

4/2/2007
Date

Moo-Jhong Rhee, PhD
Branch Chief

4/2/2007
Date

Establishment Information:

Prilosec® (omeprazole magnesium) For Delayed-Release Oral Suspension (NDA 22-056)

Site Name/Address	Name of Contact and Telephone Number	Registration Number (CFN)	Drug Master File Number	Primary Responsibility	Inspection Ready
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AstraZeneca AB Kvarnbergagatan 12 SE-151 85 Södertälje Sweden	John Grazal, Senior Director Global Compliance Management (302) 886-3527	CFN: Not applicable FEI: 3002806411	12726	Manufacture of drug substance omeprazole magnesium	Yes
AstraZeneca AB Gärtunavägen 151 85 Södertälje Sweden	John Grazal, Senior Director Global Compliance Management (302) 886-3527	CFN: 9612468 FEI: 3002806411	12694	Manufacture of omeprazole delayed release granules and drug product Prilosec (omeprazole magnesium) For Delayed-Release Oral Suspension	Yes

b(4)

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

/s/

Marie Kowblansky
4/5/2007 05:37:45 PM
CHEMIST

Moo-Jhong Rhee
4/6/2007 08:51:08 AM
CHEMIST
Chief, Branch III