CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-229

CHEMISTRY REVIEW(S)
ADDENDUM

Date: May 5, 2005
From: Maria Ysern, MSc, Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Through: Liang Zhou, PhD, Division of Gastrointestinal and Coagulation Drug products, HFD-180
To: NDA 21-229

It was brought to our attention that in section 16 of the review (Chemical Name, Structural Formula) the name Omeprazole magnesium was inadvertently substituted by Esomeprazole. This has been corrected, see addendum to the review.
NDA 21-229

PRILOSEC OTC™

The Procter & Gamble Co, Agent
Astra Zeneca LP, Sponsor

Maria E. Ysern

Division of Gastrointestinal and Coagulation Drug Products
Table of Contents

Table of Contents .............................................................................................................. 3

Chemistry Review Data Sheet ............................................................................................. 4

The Executive Summary ...................................................................................................... 8

I. Recommendations ........................................................................................................ 8
   A. Recommendation and Conclusion on Approvability .................................................. 8
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk
      Management Steps, if Approvable .............................................................................. 8

II. Summary of Chemistry Assessments .............................................................................. 8
   A. Description of the Drug Product(s) and Drug Substance(s) ........................................ 8
   B. Description of How the Drug Product is Intended to be Used ................................... 8
   C. Basis for Approvability or Not-Approval Recommendation ...................................... 9

III. Administrative ............................................................................................................. 9
   A. Reviewer’s Signature .................................................................................................. 9
   B. Endorsement Block .................................................................................................. 9
   C. CC Block ................................................................................................................ 9

Chemistry Assessment ....................................................................................................... 10

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .... 10
   S  DRUG SUBSTANCE [Name, Manufacturer] ............................................................... 10
   P  DRUG PRODUCT [Name, Dosage form] ................................................................. 10
   A  APPENDICES ........................................................................................................ 11
   R  REGIONAL INFORMATION .................................................................................. 11

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 .......................... 12
   A. Labeling & Package Insert ..................................................................................... 12
   B. Environmental Assessment Or Claim Of Categorical Exclusion .............................. 12

III. List Of Deficiencies To Be Communicated .................................................................. 12
Chemistry Review Data Sheet

1. NDA or ANDA 21-229

2. REVIEW # 1 (Resubmission)

3. REVIEW DATE: April 16, 2003

4. REVIEWER: Maria E. Ysern, MSc.

5. PREVIOUS DOCUMENTS:

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<td>Mar 7, 2003</td>
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7. NAME & ADDRESS OF APPLICANT:
Name: The Procter and Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio
45040-9462

Representative: Douglass Ws. Bierer, PhD
Director, Regulatory Affairs.

Telephone: 513-622-2314

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: PRILOSEC OTC™
   b) Non-Proprietary Name (USAN): Omeprazole Magnesium Delayed-Release Tablets
   c) Code Name/# (ONDC only):
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 2,3 S
      • Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION:
   N/A

10. PHARMACOL. CATEGORY: Proton Pump Inhibitor.
    Indication: Acid reducer. Treatment of frequent heartburn.

11. DOSAGE FORM:
    Delayed release tablets.

12. STRENGTH/POTENCY:
    20 mg

13. ROUTE OF ADMINISTRATION:
    Oral

14. Rx/OTC DISPENSED: ___Rx ___X_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:

Correction: Should have said: Omeprazole Magnesium

![Chemical Structure]

5-Methoxy-2-[[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-benzimidazole, magnesium salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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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:

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18. STATUS:

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The Chemistry Review for NDA 21-229

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   From the standpoint of CMC this application can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:
   None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
   Drug Substance:
   Omeprazole magnesium. This is the magnesium salt of Omeprazole, approved as Prilosec. Description provided in DMFs and

   The same formulations were used for preclinical and marketing.

   Drug Product:
   The drug product consist of a number of enteric –coated pellets compressed into a tablet. The applicant calls this a “Multiple Unit Pellet System”(MUPS Tablet).
   Strength: 20 mg.
   Formulation and drug product manufacturing is described in DMF

B. Description of How the Drug Product is Intended to be Used
   This product is for adults (18 years and older) with frequent heartburn (heartburn 2 or more days a week). It is not intended for those who have heartburn infrequently (one episode of heartburn per week or less, or for those who want immediate relief
First course of treatment is to swallow one 20 mg tablet with a glass of water before eating in the morning. Take everyday for 14 days, no more than one tablet per day. The same 14 day course of therapy may be repeated every 4 months. For more than 14 days or more often than 4 months needs to be directed by a physician. It is important not chew or crush the tablets or crush the tablets in food.

Expiration dating period and recommended storage conditions: 24 months, Store at [USP controlled room temperature].

C. Basis for Approvability or Not-Approval Recommendation

The pending labeling comments have been addressed. From the standpoint of CMC this application can be approved.

III. Administrative

A. Reviewer’s Signature
   See DFS

B. Endorsement Block

   Chemist Name/Maria Ysern, MSc.
   Chemistry Team Leader/Liang Zhou, PhD
   Project Manager Name/Melissa Furness

C. CC Block
   See DFS
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------------
Maria Ysern
5/5/05 12:44:58 PM
CHEMIST

Liang Zhou
5/5/05 02:22:00 PM
CHEMIST
**Establishment Evaluation Request**

**Summary Report**

- **Application:** NDA 21229/000
- **Org Code:** 180
- **Priority:** 23S
- **Stamp Date:** 27-JAN-2000
- **PDUPA Date:** 20-JUN-2003
- **Action Goal:** 20-JUN-2003
- **District Goal:** 28-SEP-2000
- **Brand Name:** PRILosec 1 (Omeprazole Magnesium) 20MG Tab
- **Generic Name:** Omeprazole Magnesium
- **Dosage Form:** Delayed Release Tablet
- **Strength:** 20 MG

**FDA Contacts:**
- M. WALSH
  - Project Manager (HFD-103)
  - 301-827-3959
- A. SHAW
  - Review Chemist (HFD-800)
  - 301-827-5918
- L. ZHOU
  - Team Leader (HFD-180)
  - 301-827-1251

**Overall Recommendation:**

- ACCEPTABLE on 14-APR-2003 by J. D. AMBROGIO (HFD-322) 301-827-9049
- ACCEPTABLE on 09-OCT-2002 by S. FERGUSON (HFD-322) 301-827-9009
- ACCEPTABLE on 18-SEP-2000 by J. D. AMBROGIO (HFD-322) 301-827-9049

**Responsibilities:**

- **Profile:** TCT
  - **OAI Status:** NONE

- **Last Milestone:** QC Recommendation
- **Milestone Date:** 16-MAR-00
- **Decision:** ACCEPTABLE
- **Reason:** BASED ON PROFILE

- **Profile:** CTL
  - **OAI Status:** NONE

- **Last Milestone:** QC Recommendation
- **Milestone Date:** 16-MAR-00
- **Decision:** ACCEPTABLE
- **Reason:** BASED ON PROFILE

**Establishment:**

- AADA:

- **DMF No.:**

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**Establishment:**
- CFN: 9615999
- FEI: 3003342394
- AASTRA PRODUCTION TABLETS AB
- GARTUNAVAGAN
- SODERTALJE, SW SK102NA

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**Establishment:**
- CFN: 1012256
- FEI: 1012256
- MERCK AND CO INC
- 3517 RADIUM SPRINGS RD
- ALBANY, GA 31708

 DMF No: [ ] AADA:

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**Establishment:**
- CFN: 1017175
- FEI: 1017175
PROCTER AND GAMBLE MFG CO  
100 SWING ROAD  
GREENSBORO, NC 27409  

Responsibilities: FINISHED DOSAGE PACKAGER  
Profile: TCT  
OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 07-JUL-00  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION  

Establishment: CFN:  
FEI:  

Responsibilities:  
Profile: TCT  
OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 14-APR-03  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION  

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3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maria Ysern
4/24/03 02:30:44 PM
CHEMIST

Liang Zhou
4/24/03 02:54:37 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL
NDA 21-229

Prilosec 1

Arthur B. Shaw, Ph.D.

Division of Gastrointestinal and Coagulation Drug Products
Table of Contents

Table of Contents ............................................................ 2

Chemistry Review Data Sheet .................................................. 3

The Executive Summary ......................................................... 6

I. Recommendations .................................................................. 6

A. Recommendation and Conclusion on Approvability: .................. 6

B. Recommendation on Phase 4 (Post-Marketing) Commitments,
   Agreements, and/or Risk Management Steps, if Approvable: 6

II. Summary of Chemistry Assessments ..................................... 6

III. Administrative ................................................................... 6

A. Reviewer's Signature: See DFS ........................................... 6

B. Endorsement Block R/D/ init by Liang Zhou 05-Aug-2002 .... 6

C. CC Block: See DFS ............................................................... 6

Chemistry Assessment .............................................................. 7
Chemistry Review Data Sheet

1. NDA 21-229
2. REVIEW #: 2
3. REVIEW DATE: August 2
4. REVIEWER Arthur B. Shaw, Ph.D.
5. PREVIOUS DOCUMENTS:
   Original 27-Jan-2000
   REVIEW #1 02-Nov-2000
   DR Letter 02-Nov-2000
   Telecom 13-Nov-2000
   NA Letter 27-Nov-2000
6. SUBMISSION BEING REVIEWED:
   Amendment BC 15-Nov-2000
   Amendment AZ 12-Feb-2002

7. NAME & ADDRESS OF APPLICANT:
   Name: AstraZeneca LP
   Address: 155725 Chesterbrook Blvd
             Wayne PA 19087-5677
   Representative: Gary Horowitz

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Prilosec 1 Note that the applicant was
      informed that this name was not acceptable in the NA letter.
      They have not responded satisfactorily to this.
   b) Non-Proprietary Name (USAN): Omeprazole magnesium
   c) Code Name/# : N/A
   d) Chem. Type/Submission Priority
      • Chem. Type 1
      • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: New drug
10. PHARMACOL. CATEGORY: Proton pump inhibitor
11. DOSAGE FORM: Delayed release tablet
12. STRENGTH/POTENCY: 20 mg

13. ROUTE OF ADMINISTRATION Oral
14. Rx/OTC DISPENSED: _Rx _X_OTC
15. _X Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT
   N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-), magnesium salt, trihydrate
(C_{17}H_{18}N_{3}O_{5}S)_{2}\text{Mg}

CAS Number: 5382-33-5

MW: and 713.1 g/mol

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17. RELATED/SUPPORTING DOCUMENTS

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The Chemistry Review for NDA 21-229

The Executive Summary

I. Recommendations
A. Recommendation and Conclusion on Approvability:
   Approvable. There are two labeling comments.
B. Recommendation on Phase 4 (Post-Marketing) Commitments,
   Agreements, and/or Risk Management Steps, if Approvable:
   None

II. Summary of Chemistry Assessments
A. Description of Drug Product and Drug Substance:
   - Drug Product Description: The drug product consists of a
     number of enteric-coated pellets compressed into a
     tablet. The applicant calls this a "Multiple Unit
     Pellet System" = MUPS Tablet. There is only one
     strength, 20 mg
   - Drug Substance Description: Omeprazole magnesium. This
     is the magnesium salt of omeprazole, approved as
     Prilosec. Described in DMFs — and —
   - Formulation and Drug Product Manufacturing: Described
     in DMF —
   - Comparison of Preclinical and Marketing Formulations:
     The same formulations were used for preclinical and
     marketing.
   - Additional Drug Product Information:
     All of the information regarding the drug substance and
     drug product are contained in DMFs.
B. Description of How the Drug Product is Intended to be
   Used:
   - Recommended dosage:
     20 mg once a day for treatment of heartburn. The drug
     is not intended for treatment of episodic heartburn.
   - The drug product is not intended for co-administration
     with another drug.
   - Intended for OTC use
   - Expiration dating period and recommended storage
     conditions. 24 months, USP Controlled room temperature

III. Administrative
A. Reviewer's Signature: See DFS
B. Endorsement Block R/D/ init by Liang Zhou 05-Aug-2002
C. CC Block: See DFS
3 Page(s) Withheld

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☐ § 552(b)(5) Deliberative Process

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/s/

Arthur B. Shaw  
8/7/02 11:28:54 AM  
CHEMIST

Liang Zhou  
8/7/02 04:22:27 PM  
CHEMIST

APPEARS THIS WAY  
ON ORIGINAL
NDA #21-229

Drug Product Proprietary Name: Prilosec 1

USAN Name: esomeprazole magnesium

Chemical Type/Therapeutic Class: 18

Type of Letter: Not Approvable

Tertiary Chemistry Review #1

EA: Acceptable. See E-mail review addendum dated 14 November 2000.

EER: EER Summary Report dated 31 October 2000 lists all sites as ACCEPTABLE.

Microbiology: Not Applicable. Solid Oral Dosage form.

Trade Name: Under review by OPDRA. Review chemist recommends "delayed release" between "omeprazole" and "tablets" on the PI, carton, and blister labeling.

Methods Validation: Unsatisfactory. Applicant has not supplied a set of specifications for drug substance or drug product in this application. Additionally, the applicant has not submitted a complete methods validation package.

CMC: Chemistry Review #1 dated 30 October 2000 found the information presented in DMFs and for the drug substance to be adequate. However this chemistry review also states that the information in DMF was found not adequate in a review dated 11 October 2000 and a deficiency letter was sent on 12 October 2000. Additionally DMFs and for blister packaging components were also found not adequate.

The chemistry review of this NDA also states that the complete drug substance and drug product specifications should be included in this NDA.

The conclusion of Chemistry Review #1 is that this NDA is APPROVABLE.

John J. Gibbs, Ph.D.
Director, Chemistry Division II
/s/
--------------------------------
John J. Gibbs
11/21/00 02:17:01 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls


4. SUBMISSIONS REVIEWED
   DOCUMENT  CDER  ASSIGNED

5. NAME & ADDRESS OF APPLICANT:
   AstraZeneca LP
   725 Chesterbrook Blvd
   Wayne PA 19087-5677

6. DRUG PRODUCT NAME:
   Proprietary: Prilosec
   Nonproprietary/USAN: omeprazole magnesium
   Chem.Type/Ther.Class: 1S
   Code names: H 199/18

7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor

8. INDICATION: Treatment and prevention of heartburn

9. DOSAGE FORM: delayed release tablet

10. STRENGTH: 20 mg

11. ROUTE OF ADMINISTRATION: oral

12. HOW DISPENSED: Rx X OTC

13. CHEMICAL IDENTIFICATION:

   N Bis (1H-Benzimidazole, 5-methoxy-2-[(S)-[4-methoxy-3,5-
   dimethyl-2-pyridinyl)methyl)sulfinyl]-), magnesium salt,
   trihydrate
   (C₁₇H₁₈N₃O₅S)₂Mg x 3H₂O
   CAS Number 217087-09-7
   MW= 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

15. RELATED DOCUMENTS NDA 19-810

16. CONSULTS: None

17. REMARKS/COMMENTS: The DMF reviews for the drug substance are considered "Acceptable." However the DMF for the drug product, —, was found to be inadequate in a review dated October 11, 2000. A deficiency letter was sent on October 12, 2000. The applicant should provide the specifications and test methods in the NDA, updated to reflect changes in the DMFs. There are deficiencies in the DMFs for some of the packaging components.

17. CONCLUSIONS & RECOMMENDATIONS: Approvable. The applicant should be sent a Discipline Review Letter.

[Signature]
Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

[Signature]
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 21-229
HFD-180/Division File/NDA 21-229
HFD-181/CSO
HFD-180/LTalarico
HFD-180/LZhou
HFD-180/HGallo-Torres
HFD-180/ASHaw
R/D Init by: LZhou 31-Oct-2000
f/t/ABS 31-Oct-2000
C:\Final\21229 Prilosec 1 Chem Review #1.doc
A. **DRUG SUBSTANCE:** All information in DMFs — and —

The DMFs are **ACCEPTABLE**.

B. **DRUG PRODUCT:** All information in DMF —. The DMF is not acceptable. The applicant has provided a table of "Specifications" on Page 11 of Volume 1.004 of the NDA.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>A pink, oblong, biconvex, film-coated tablet debossed Pl on one side</td>
</tr>
<tr>
<td>Identity Omeprazole</td>
<td>Positive</td>
</tr>
<tr>
<td>Identity Mg Omeprazole</td>
<td>Positive</td>
</tr>
<tr>
<td>Omeprazole Content</td>
<td>100% of stated amount*</td>
</tr>
<tr>
<td>Content Uniformity (omprazote)</td>
<td>Meets USP</td>
</tr>
<tr>
<td>Drug Release</td>
<td>Q NLT —after— minutes using USP &quot;Drug release-Enteric coated articles, buffer stage&quot; at — rpm in Dissolution</td>
</tr>
<tr>
<td>Related substances Total</td>
<td>NMT</td>
</tr>
<tr>
<td>Any single known substance</td>
<td>NMT</td>
</tr>
<tr>
<td>Any single unknown substance</td>
<td>NMT</td>
</tr>
</tbody>
</table>

The specifications were discussed in the review of DMF — and found to be not acceptable. There were a number of other parts of the DMF for which more information is required.

**COMMENT:** The applicant should be advised that DMF — for the drug product is not acceptable.
C. CONTAINER/CLOSURE SYSTEM: The drug product will be packaged in _______ and a _______ (one tablet per pouch, for promotional purposes).

<table>
<thead>
<tr>
<th>Component</th>
<th>Manufacturer</th>
<th>DMF</th>
<th>LOA Date</th>
<th>Page</th>
<th>Item Referenced</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>23-Jul-99</td>
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<td>18</td>
<td>Sec 107</td>
<td>Adequate 25-Oct-1999 Sue-Ching Lin</td>
<td></td>
</tr>
</tbody>
</table>

COMMENT: The applicant should be informed that DMFs _____ and _____ for blister packaging components were found to be inadequate.

D. LABELING: The Division of OTC drugs and OPDRA are reviewing most aspects of the labeling. The only chemistry issues are:

1. The name of the active ingredient:
   
   This is "omeprazole magnesium 20.6 mg (equivalent to 20 mg)." ACCEPTABLE

2. There is a statement "Do not chew or crush tablet." This is appropriate since this is a delayed-release formulation. ACCEPTABLE

3. The Carton and Package Insert name the drug as:

\[
\text{The blister backing states:} \quad \text{APPEARS THIS WAY ON ORIGINAL}
\]

The words "delayed release" should appear in the title.
COMMENT: The applicant should be advised to add the words "delayed Release" between "omeprazole" and "tablets" in the Carton Label, Package Insert, and Blister labeling.

E. ESTABLISHMENT INSPECTION

All sites are ACCEPTABLE See Appendix

F. LIST OF CHEMISTRY DEFICIENCIES AND COMMENTS:

1. You are advised that DMF — for the drug product is not acceptable.

2. Provide a complete set of specifications for the drug substance and the drug product in the NDA. Also provide a complete methods validation package.

3. You are advised that DMFs — and — for materials used in the blister packages have been found to be deficient and the holders have been notified.

4. You are advised to add the words "delayed Release" between "omeprazole" and "tablets" in the Carton Label, Package Insert, and Blister labeling.
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21229/000
Applicant: ASTRAZENECA
725 CHESTERBROOK BLVD
WAYNE, PA 190875077

Priority: 235
Org Code: 180

Action Goal: 28-SEP-2000

Brand Name: PRILOSEC HOMEPEPRAZOLE MAGNESIUM 20MG TAB

Established Name: OMEPRAZOLE MAGNESIUM

Dosage Form: DRT (DELAYED RELEASE TABLET)

Strength: 20 MG

FDA Contacts:
M. WALSH (HFD-180) 301-827-7310, Project Manager
A. SHAW (HFD-180) 301-827-7310, Review Chemist
L. ZHOU (HFD-150) 301-594-5765, Team Leader

Overall Recommendation:
ACCEPTABLE on 18-SEP-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Profile: TCT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-MAR-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-MAR-2000
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 30-AUG-2000
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<td>SODERTALJE, SW</td>
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<td>100 SWING ROAD</td>
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<td>GREENSBORO, NC 27409</td>
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APPEARS THIS WAY ON ORIGINAL